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Research Article

STUDY OF PLATELET INDICES AS MARKERS OF CARDIOVASCULAR RISK IN PATIENTS OF CHRONIC KIDNEY DISEASE

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A R T I C L E I N F O

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A B S T R A C T

Background: Chronic kidney disease (CKD) is now recognized as a leading public health burden with a prevalence of approximately 13.4%. Cardiovascular disease is the most common cause of mortality in CKD patients before reaching ESRD. Hence early detection of the cardiovascular disease in CKD is of paramount importance in order to reduce mortality in CKD patients. As platelet activation results in thrombosis, hence platelet indices are indicators of platelet activation and marker of thrombotic events and development of cardiovascular disease.

Objectives: To study the various platelet indices (TPC,MPV,PDW,PCT and PLCR) and cardiovascular diseases in CKD patients and correlation between them.

Materials and methods: We performed a single-centre analytical cross-sectional study involving 230 CKD patients admitted in General Medicine and Nephrology wards of VIMSAR, Burla over a period of 2 years to explore the relationship between platelet indices and CVD events in CKD patients Patients were categorised into various stages after GFR estimation with CKD-EPI equation. The association of platelet indices and the various cardiovascular diseases in CKD was then evaluated by various tables, graphs and charts. Finally ROC curves were applied to evaluate the predictive accuracy of platelet indices on CVD risk in CKD patients.

Results: During our 2 years study period,158(68.6%) out of the 230 CKD had developed CVD and abnormal platelet indices was found in 55.2% of CKD patients. Results showed that TPC,MPV and PDW were significantly associated with overall development of CV events in CKD patients(p values of 0.001,<0.001,<0.001 respectively). MPV was the most predictive and early indicator of the risk of development of various cardiovascular disease in CKD followed by PDW,TPC,PCT and PLCR.

Conclusion: We demonstrated that TPC,MPV and PDW were independently associated with CVD in CKD patients. PCT was independently associated with HTN in CKD patients. MPV, PDW, PCT and PLCR were independently associated with MI in CKD patients. MPV and PDW were independently associated with DCM in CKD patients. MPV was the best and earliest indicator of CVD risk in CKD patients.

INTRODUCTION

Chronic kidney disease encompasses a spectrum of pathological processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate. According to the KDIGO revised definition – CKD is defined as abnormality of kidney structure or function, present for >3 month, with implication for health.(1) Criteria for CKD: Either of following present for >3 month:

Marker of kidney damage

- Albuminuria
- Urinary sediment abnormalities
- Electrolyte and other abnormality due to tubular disorder
- Structural abnormality detected by imaging
- Abnormality detected by histology
- History of kidney transplantation

Decreased Glomerular Filtration Rate-GFR <60 ml/min/1.73 m^2 (2)

Chronic kidney disease (CKD) is now recognized as a leading public health burden with a prevalence of approximately 13.4%, which affects more than 1 billion people around the world(3). The approximate prevalence of CKD in India is 800 per million population (PMP) and the incidence of ESRD is 150 – 200 PMP.(4)

Vascular causes of CKD are renal artery stenosis, vasculitis, atheroembolic renal disease and hypertensive nephrosclerosis. Patients with CKD are more prone for CVD and the incidence increases with declining renal function.(5)

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Cardiovascular disease is the leading cause of morbidity and mortality in patients at every stage of CKD. The pathogenesis of heart–kidney interactions involves both traditional and non-traditional cardiovascular risk factors. General risk factors include age, abnormal blood lipids, and high blood pressure, as well as oxidative stress, endothelial dysfunction, chronic inflammation, and advanced glycation end-products[(6)]. Because of the multifactorial pathogenesis, treating patients with CKD and concomitant CVD is challenging. Therefore, early identification and effective targeted intervention are essential to retard the progression of CKD and reduce cardiovascular morbidity and mortality.

As platelet activation results in thrombosis, hence platelet indices are indicators of platelet activation and marker of thrombotic events and development of cardiovascular disease.[(7)] Mean platelet volume (MPV), the most commonly investigated platelet parameter, signifies the average size of platelets in the blood. In healthy subjects it typically ranges between 6.5 and 12 fL. MPV of over 13 fL tends to occur in hyperdestruction, in which case young platelets become bigger and increase in activity, whereas MPV lower than 8 fL is a sign of platelet hypoproduction [(8)]. Larger platelets are metabolically and enzymatically more active and this increased activity is linked to increase in cardiovascular risk.[(9)] It was observed in patients suffering from myocardial infarction, that those with higher MPV level seemed to be more often associated with poor clinical outcome. Lower MPV level can be related to low-grade inflammation, such as rheumatoid arthritis [(10)].

Platelet distribution width (PDW) is a marker of platelet anisocytosis, which describes the size distribution of platelets produced by megakaryocytes and increases upon platelet activation. The normal value of PDW ranges between 15-17fL. Platelet distribution width is analyzed by average size of platelets. PDW seems to be proportionally related to MPV in healthy individuals [(11)].

Platelet larger cell ratio (P-LCR), another marker of platelet activity, is a percentage of all platelets with a volume measuring over 12 fL circulating in the bloodstream.[(12)] It normally ranges between 11 and 45%. Plateletcrit (PCT) measures total platelet mass as a percentage of volume occupied in the blood. The normal range for PCT is 0.108-0.282% . Plateletcrit is the ratio of platelet volume to the whole blood volume.

PCT=MPV/TPC
PCT is calculated by using the following formula: PCT=platelet count×MPV [(13)].

PI can be measured inexpensively and are accessible at hand during routine blood counts. Previous studies mainly reported that the relationship between MPV and CVD events existed in the non-CKD population. The association between the rest platelet indices and CVD events in patients with CKD has not been thoroughly evaluated. Thus, this study aims to investigate the relationship between platelet indices and CVD events in CKD patients.

Aims And Objectives- To study the various platelet indices (TPC, MPV,PDW,PCT and PLCR) and cardiovascular diseases in CKD patients and correlation between them.

MATERIAL AND METHODS

Place of Study: Department of General medicine and Department of Nephrology, VIMSAR, Burla

Study Period: 2 Years (January 2021-December 2022)

Study Design: Observational cross-sectional analytical study.

Study Population: In-patients of dept. of general medicine and department of nephrology who are diagnosed with chronic kidney disease

Sample Size Estimation: 230 cases of chronic kidney disease which included those who had cardiovascular disease and those who did not have cardiovascular disease.

Calculated by using the formula - $4PQ/L^2$
P=Prevalence, Q=1-P, L=Absolute Error
From previous study, prevalence(P) =13.4%
Q=86.6
L=5%
Sample size(n)=186
Hence minimum sample size needed is 186. But we have taken 230 patients of CKD in our study.

Subject Selection

Inclusion criteria

Diagnosed cases of chronic kidney disease aged >14yrs admitted to general medicine and nephrology wards.

Exclusion criteria

- Acute kidney injury
- Patients with previous CVD, Hypertension, coronary artery disease
- Type 2 Diabetes Mellitus
- Acute stroke
- Sepsis
- Active malignancy
- Abnormal platelet disorders-ITP
- Patients on antiplatelet drugs
- Patients on antihypertensive drugs

MATERIALS AND METHODS

We performed a single-center analytical cross-sectional study involving 230 CKD patients admitted in General Medicine and Nephrology wards of VIMSAR, Burla over a period of 2 years to explore the relationship between platelet indices and CVD events in CKD patients. They were evaluated extensively by history, clinical examination, routine investigations which included CBC (containing platelet indices TPC,MPV, PDW, PCT,PLCR), RFT, Sr.electrolytes, lipid profile, etc., followed by USG abdomen and pelvis, ECG and 2D-ECHO and Troponin I quantitative estimation. Patients were categorised into various stages after GFR estimation with CKD-EPI equation. The association of platelet indices and the various cardiovascular diseases in CKD was then evaluated by various tables, graphs and charts. Finally ROC curves were applied to evaluate the predictive accuracy of platelet indices on CVD risk in CKD patients. Observed data was collected, compiled, evaluated and after matching baseline characteristics, all data was analysed using MS Excel, SPSS 21 software.

RESULTS

Table 1 showing the association of various platelet indices with CVD in CKD patients

	Cardiovascular Abnormalities		
	YES	NO	p-value
TPC	250 [188-519]	204 [156-295]	0.001
MPV	12.40 [10.40-12.80]	9.50 [8.60-10.40]	<0.001
PDW	17.20 [16.10-17.40]	16.00 [15.50-16.50]	<0.001
PCT	0.21 [0.16-0.30]	0.20 [0.15-0.27]	0.209
PLCR	30.60 [23.80-36.70]	30.00 [24.75-36.15]	0.576

Median value of TPC, MPV, PDW among CKD patients with cardiovascular events was 250x10^3/µL,12.4fL and 17.2fL respectively which was higher than those who had no cardiovascular event. Hence higher TPC, MPV and PDW was associated with cardiovascular events which was statistically significant with p value of 0.001,<0.001 and <0.001respectively.

No significant difference in PCT and PLCR among CKD patients who developed cardiovascular event.

Table 2 Showing association of platelet indices and cardiovascular events (Hypertension, Concentric LVH and Dyslipidemia) in CKD patients

	HTN	P value	Concentric LVH	P value	Dyslipidemia	P value
TPC	224 [177-428]	0.363	241 [195-512]	0.153	251 [176-450]	0.236
MPV	12.15 [9.40-12.60]	0.541	11.30 [8.50-12.40]	0.099	12.30 [9.90-12.70]	<0.001
PDW	16.90 [16.00-17.35]	0.133	16.40 [16.00-17.20]	0.749	17.10 [16.00-17.40]	0.002
PCT	0.20 [0.15-0.25]	0.005	0.20 [0.18-0.23]	0.376	0.22 [0.16-0.30]	0.049
PLCR	31.50 [24.25-36.65]	0.663	28.10 [23.40-34.20]	0.061	34.00 [25.00-39.20]	0.018

Among these indices, only PCT was having significant statistical difference among CKD patients with HTN with p value of 0.005. None of the platelet indices had any significant difference among CKD patients who had Concentric LVH on 2D ECHO. The various lipid abnormalities encountered in CKD patients included increase in TG, LDL, & cholesterol and decrease in HDL levels. Higher MPV, PDW, PCT and PLCR were found to be significantly associated with dyslipidemia with p values of <0.001,0.002,0.049 and 0.018 respectively.

Table 3 showing the association of various platelet indices with development of myocardial infarction in patients with CKD

	Myocardial Infarction	pvalue	Anterior Wall mi	pvalue	Inferior Wall mi	pvalue
TPC	276 [193-436]	0.363	314 [193-436]	0.542	259 [194-421]	0.461
MPV	12.50 [12.30-13.10]	<0.001	12.50 [12.30-13.10]	<0.001	12.55 [12.40-13.20]	0.002
PDW	17.20 [16.30-17.30]	0.010	17.20 [16.30-17.30]	0.055	17.20 [16.90-17.30]	0.136
PCT	0.25 [0.18-0.32]	0.003	0.24 [0.17-0.30]	0.173	0.30 [0.22-0.35]	0.002
PLCR	34.00 [28.40-42.20]	0.029	34.70 [28.40-44.20]	0.032	34.05 [29.00-26.45]	0.350
Troponin I	1.40 [1.20-1.80]	<0.001	1.40 [1.20-1.80]	<0.001	1.40 [1.20-1.80]	<0.001

Higher MPV, PDW, PCT and PLCR was found to be significantly associated with MI in CKD patients with p-values of <0.001,0.010,0.003, and 0.029 respectively. Higher MPV and PLCR was found to be significantly associated with anterior wall MI with p-values of <0.001, and 0.032 respectively. Higher MPV and PCT was found to be significantly associated with inferior wall MI with p-values of 0.002, and 0.002 respectively.

Table 4 Showing the association of various platelet indices with development of dilated cardiomyopathy and arrythmia in patients with CKD

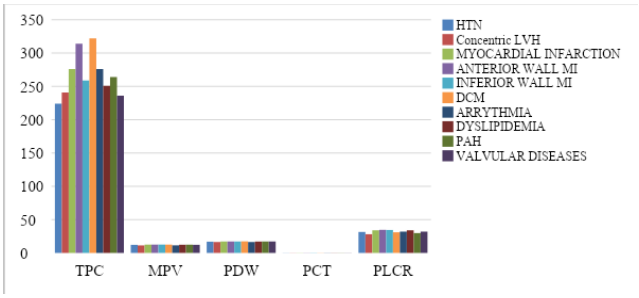
	Dcm	p-value	Arrythmia	p-value
TPC	322 [163-523]	0.115	276 [203-512]	0.379
MPV	12.50 [12.20-13.10]	<0.001	11.40 [9.50-12.50]	0.811
PDW	17.40 [17.10-17.55]	<0.001	16.40 [15.60-17.60]	0.660
PCT	0.24 [0.15-0.32]	0.135	0.22 [0.20-0.32]	0.153
PLCR	31.00 [28.00-35.40]	0.415	32.00 [24.90-38.60]	0.697

MPV and PDW were found to be significantly higher in CKD patients having DCM with p-values of <0.001 and <0.001 respectively. Arrhythmia was seen in 8.3% patients of CKD in our study. There is no significant difference of any of the platelet indices among CKD patients with arrhythmia.

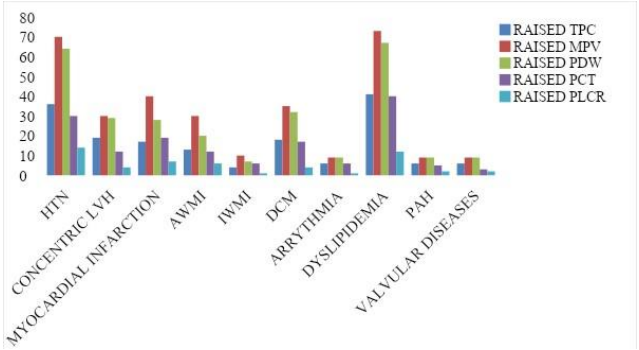
Table 5 showing the association of platelet indices with development of pulmonary artery hypertension and valvular heart diseases in patients with CKD

	PAH	p-value	Valvular Diseases	p-value
TPC	264 [167-546]	0.486	236 [224-532]	0.126
MPV	12.40 [9.20-12.80]	0.276	12.20 [9.90-12.40]	0.631
PDW	17.20 [16.00-17.50]	0.266	17.20 [16.20-17.40]	0.304
PCT	0.24 [0.11-0.30]	0.810	0.21 [0.19-0.26]	0.687
PLCR	29.80 [19.60-42.00]	0.876	32.00 [28.10-39.40]	0.293

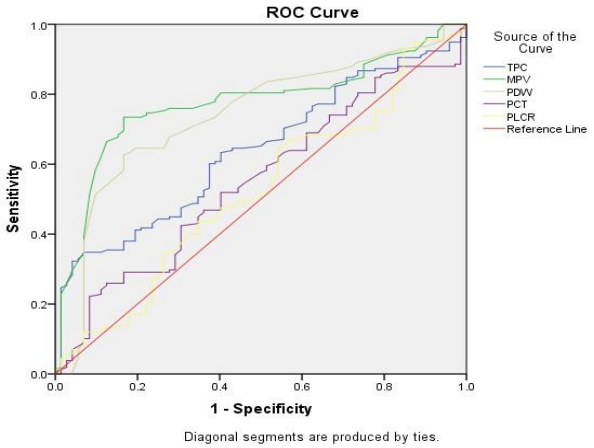
There is no significant difference of any of the platelet indices among CKD patients with PAH. There is no significant difference of any of the platelet indices among CKD patients with valvular heart diseases.



Graph 1 Variation of Platelet indices among different Cardiovscular Diseases in CKD



Graph 2 showing the Prevalence of raised platelet indices in various cardiovascular abnormalities seen in CKD



Graph 3 Prediction of cardiovascular diseases in CKD using platelet indices - Area Under the Curve

Table 6 showing the various result variable and Area Under the Curve

Test Result Variable(s)	Area
TPC	.638
MPV	.773
PDW	.739
PCT	.552
PLCR	.523

The test result variable(s): TPC, MPV, PDW, PCT, PLCR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

Predictive Analysis -Receiver's operating chart (ROC) was plotted between all platelet indices and CVD events, to find out which parameter was significantly predicting the development of cardiovascular disease in later stage of disease. The analysis method used was AUC (area under curve) i.e., the parameter which had larger AUC will predict the risk to develop cardiovascular disease. Based upon the analysis, the area under curve of TPC, MPV, PDW, PCT and PLCR was 0.638, 0.773, 0.739, 0.552 and 0.523 respectively. From analysis, it was observed that mean platelet volume predicted the development of cardiovascular disease early compared to other indices, which indicated that those who had high value of MPV were more likely to develop cardiovascular disease at a later stage of disease.

DISCUSSION

The pathogenesis of CVD and CKD has several similar characteristics. Both CVD and CKD promote each other. Thus, understanding their interactions will greatly improve the prevention, diagnosis, and treatment of both diseases.[14] In our current study, we investigated the association between platelet indices and CVD events in CKD patients.

Higher TPC, MPV and PDW were associated with cardiovascular events which was statistically significant with p value of 0.001,<0.001 and <0.001respectively. No significant difference in PCT and PLCR among CKD patients who developed cardiovascular event. This was in concordance with study conducted by Yu Zhakai et al. which also showed significant association of TPW and PDW with cardiovascular event in CKD patients with p value of <0.001 and 0.005 respectively.[15]

Among these indices, only PCT was having significant statistical difference among CKD patients with HTN with p value of 0.005. None of the platelet indices were having any significant differences among CKD patients with concentric LVH on 2D ECHO. Study conducted by CJ Boos et al. demonstrated higher MPV and PDW to be significantly associated with HTN with p values of <0.001 and 0.001 respectively.[16]

Higher MPV, PDW, PCT and PLCR was found to be significantly associated with MI in CKD patients with p-values of <0.001,0.010,0.003, and0.029 respectively. Higher MPV and PLCR was found to be significantly associated with anterior wall MI with p-values of <0.001, and 0.032 respectively. Higher MPV and PCT was found to be significantly associated with inferior wall MI with p-values of 0.002, and 0.002 respectively. Turk Ugur et al.'s study demonstrated no statistical difference for TPC, MPV, PDW values among STEMI, UA, and NSTEMI patients[17].

MPV and PDW were found to be significantly higher in CKD patients having DCM with p-values of <0.001 and <0.001 respectively. Dahlen Bianca et al.'s study demonstrated higher MPV to be significantly associated with HFrEF which was similar to our study results[18]. The most common arrhythmia encountered in CKD patients was atrial fibrillation which was seen in 6.1% of CKD patients. There is no significant difference of any of the platelet indices among CKD patients with arrhythmia and PAH. Varol Ercan et al.'s study showed higher MPV to be significantly associated with PAH.[19] Higher MPV, PDW, PCT and PLCR were found to be significantly associated with dyslipidemia with p values of <0.001,0.002,0.049 and 0.018 respectively.

Among the platelet indices, increased MPV was the one which was the earliest and best predictor of Cardiovascular events in CKD patients followed by PDW,TPC,PCT and PLCR as per AUC in the ROC curve. Yu Zhikai et al.'s study demonstrated higher TPC,PCT and PDW to be the most important predictors of cardiovascular event in CKD patients.[20]

Summary

Since the prevalence of CKD in Western Odisha is very high, we conducted a cross-sectional analytical study in 230 CKD patients who were admitted to Department of General Medicine and Nephrology of VIMSAR, Burla. In this study, we demonstrated how the various platelet indices could be linked to development of cardiovascular diseases in CKD. 68.6% of the CKD patients developed cardiovascular disease of which majority were males(64.6%). Mean age of presentation of Cardiovascular disease or event in CKD patients was 55.03yrs. Abnormal platelet indices (TPC, MPV, PDW, PCT and PLCR) were seen in55.2% of CKD patients. However, none of them were found to be significantly associated with stages of CKD. Higher TPC, MPV and PDW were significantly associated with cardiovascular events and diseases in CKD patients (p values of 0.001,<0.001 and <0.001respectively). Higher PCT was seen to be significantly associated with HTN in CKD patients (p value of 0.005). Higher MPV,PDW,PCT and PLCR were found to be significantly associated with development of MI in CKD patients (p value of <0.001,0.010,0.003 and0.029 respectively). Higher MPV and PLCR were significantly associated with Anterior wall MI (p values of 0.001 and 0.032

respectively) while higher MPV and PCT were significantly associated with Inferior wall MI (p values of 0.002 and 0.002respectively).

Higher MPV and PDW were found to be significantly associated with development of DCM in CKD patients (p values of 0.001 and 0.001 respectively). None of the platelet indices was found to be significantly associated with arrhythmia and PAH in CKD patients. MPV, PDW, PCT and PLCR were found to be significantly higher in patients of CKD with dyslipidemia (p values of <0.001,0.002,0.049 and 0.018 respectively). Among the platelet indices, MPV was the most predictive and early indicator of the risk of development of cardiovascular disease in CKD followed by PDW,TPC,PCT and PLCR.

CONCLUSION

In this study, we studied the various cardiovascular diseases and events which usually occur in CKD patients and demonstrated their association with the various platelet indices (TPC,MPV,PDW,PCT and PLCR). Although cardiovascular events in CKD usually occur in advanced stages of CKD (stage 4 and stage 5), however their risk can be predicted earlier using these platelet indices which can lead to earlier screening, diagnosis and treatment which will help in substantially reducing the cardiovascular mortality in CKD patients.

We demonstrated that TPC,MPV and PDW were independently associated with CVD in CKD patients. PCT was independently associated with HTN in CKD patients. MPV,PDW,PCT and PLCR were independently associated with MI in CKD patients. MPV and PDW were independently associated with DCM in CKD patients. MPV,PDW,PCT and PLCR were independently associated with dyslipidemia in CKD patients. MPV was the best and earliest indicator of CVD risk in CKD patients.

Conflict of Interest-NIL

Limitations- Relatively small number of patients were taken in this study. Healthy subjects were not included as control in our study. Hence the distribution of platelet indices could not be compared between patients having CKD to normal healthy control. CKD patients might be on drugs such as antiplatelet drugs for MI or CVA and on various other drugs that have the propensity to alter the platelet indices. But the intake of these drugs was not taken into consideration in our study.

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