Evaluation of the Relationship between Blood Cell Parameters and Vascular Calcification in Dialysis-Dependent End-Stage Renal Disease Patients

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ABSTRACT. Coronary artery calcification is an acceptable tool for cardiovascular risk assessment in end-stage renal disease (ESRD) population. We aimed to identify the association and predictive value of components of blood cell parameters with coronary and thoracic aorta vascular calcification (VC) in ESRD population on dialysis. All ESRD patients receiving hemodialysis or peritoneal dialysis aged between 18 and 60 years were included in the study. Exclusion criteria comprised patients with active infection or inflammatory disease, autoimmune disease, congestive heart failure, angina pectoris and/or documented coronary artery disease, thyroid disease, and hepatic dysfunction. Agatston scoring was used for the evaluation of coronary aorta calcification (CAC) score (CACS) and thoracic aorta calcification (TAC) score (TACS). Compared to participants with no VC, those who had VC were statistically significantly older (P < 0.001) and had higher neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) (P = 0.02 and <0.001, respectively). On multivariate logistic regression analysis, increasing age (P = 0.00) and higher PLR (P = 0.04) were associated with an increased likelihood of exhibiting VC (CAC or TAC). There was a positive correlation between CACS and age (rs = 0.495, P = 0.00). A statistically significant positive correlation existed between TACS and age (rs = 0.516, P = 0.00). Similarly, a positive correlation was found between NLR, PLR, and TACS (rs = 0.334, P = 0.001, and rs = 0.438, P = 0.00, respectively). On multivariate linear regression analysis, increased age and red cell distribution width were found to be significant predictors of log(n) TACS. PLR of 135 gave a sensitivity of 80% and a specificity of 50% for predicting VC. Being a cost-effective and easily available investigation, the utilization of the correlation of NLR and PLR with CAC and TAC appears promising, particularly in the age group of 30–60 years.

Introduction

Vascular calcification (VC) is commonly seen
in dialysis-dependent end-stage renal disease (ESRD) patients. The prevalence ranges between 35% and 70%.

Calcification affects both intimal and medial layers of the vessel wall of large arteries. It is predictive of cardiovascular mortality. Calcified vessels have increased pulse wave velocity, thereby increasing left ventricular load, subsequently causing left ventricular hypertrophy. Calcification is also progressive in nature with preexisting calcific lesions showing worsening coronary artery calcification (CAC) score (CACS). Calcification score is possibly a surrogate marker of the degree of severity of atherosclerosis in these vessels. Moreover, CAC measurement is an acceptable tool for cardiovascular risk assessment in low-to-intermediate-risk patients. Persistent inflammatory milieu in ESRD has been accounted for endothelial dysfunction, VC, and cardiovascular mortality in these patients.

Leukocyte subtypes, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and red cell distribution width (RDW) are well-known, inexpensive inflammatory biomarkers which are known to be affected by various inflammatory diseases. These have correlated well with other inflammatory markers such as C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-α in ESRD patients. However, their usefulness in predicting VC in ESRD patients has not been studied in detail. Recently, NLR measurements were shown to correlate well with VC in this population. We aimed to identify the association and predictive value of components of blood cell parameters with coronary and thoracic aorta VC in ESRD population on dialysis.

Materials and Methods

After obtaining the institute’s ethical committee approval and registering the trial with the Clinical Trials Registry-India (CTRI) (CTRI/2015/08/006115), this cross-sectional study was done at a tertiary care center. It involved ninety ESRD patients receiving hemodialysis (HD) or peritoneal dialysis (PD), aged between 18 and 60 years. It was conducted from November 2014 to February 2017. Medical details of the enrolled patients including age, sex, weight, and duration of renal replacement therapy were recorded. Patients with (a) active infection (clinically manifested as fever, cough, nausea, vomiting, diarrhea, etc.); (b) autoimmune disease or any other disease with evidence of inflammation; (c) congestive heart failure; (d) angina pectoris and/or documented coronary artery disease; (e) thyroid disease; and (f) hepatic dysfunction (including viral infections) were excluded from the study.

HD patients received thrice-weekly dialysis for a 4-h period with a standard bicarbonate containing dialysate using a biocompatible HD membrane (polysulfone, Fresenius, Germany). The dialysate flow rate was kept at 500 mL/min, and the blood flow rate was kept between 250 and 350 mL/min. The PD solutions of 1.5%/2.5% dextrose; 7.5% icodextrin (Baxter) were used.

Study of blood cell parameters – 2 mL of whole blood (venous) was collected in an ethylenediaminetetraacetic acid vacutainer at the time of admission to the study. Complete blood counts with automated differential counts were generated by a 5-part automated hematology analyzer. The differential was confirmed by manual slide review. NLR and PLR were calculated manually by absolute counts, and RDW and mean platelet volume (MPV) values were generated automatically by the instrument.

Evaluation of coronary artery calcification score and thoracic aortic calcification score

Unenhanced coronary computed tomography (CT) on electrocardiography gated cardiac CT using 64-slice multislice CT was done. CACS is defined as >2 contiguous pixels with Hounsfield units (HU) >130 as designed by Agatston et al. All values of the left anterior descending coronary artery, circumflex coronary artery, and right coronary artery were added to calculate the CACS.

Thoracic aortic calcification (TAC) score (TACS) is defined by the presence of at least three connected pixels with attenuation >130 HU. In addition, Agatston score is calculated...
by multiplying the lesion area by the attenuation score in HU.

**Statistical Analysis**

Statistical analyses were carried out using the IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Approximate normality of the continuous data was assessed using Shapiro–Wilk test. Data were expressed as mean ± standard deviation. Independent samples *t*-test was used to compare the means between two groups, whereas to compare the proportions between the groups, Chi-square test was used. If expected frequency in any cell was <5, Fisher’s exact test was used. The strength and direction of associations between CACS, TACS, and other continuous variables were assessed using the Spearman’s correlation test. TACS >10 and CACS >10 were entered as dependent variables in univariate logistic regression analysis. Then, backward elimination method was performed in the step-wise multiple logistic regression analysis. Linear regression analysis was used to identify the predictors of the outcome variables (TACS and CACS). All the significant variables found in simple linear regression were included in multivariate analysis to calculate regression coefficient and constant and corresponding significance levels. As the dependent variable data were skewed, multivariate linear regression analysis was performed after lognormal transformation of CACS and TACS. *P* <0.05 was considered statistically significant for all tests.

Receiver operative characteristics curve was used to find out the area under curve, appropriate cutoff value(s), and corresponding diagnostic accuracy of NLR and PLR to predict calcification in the study participants.

**Results**

Table 1 presents the baseline characteristics for the study participants stratified by the presence or absence of VC (CAC/TAC). Participants who had VC were statistically significantly older (*P* = 0.00) and had higher NLR, PLR, and total cholesterol levels (*P* = 0.02, 0.00, and 0.01, respectively). Hypertension was the dominant comorbidity in both the groups.

A logistic regression was performed to ascertain the effects of age, NLR, PLR, and total cholesterol levels on the likelihood that participants have CAC or TAC (Table 2). The logistic regression model explained 48.5% (Nagelkerke *R*²) of the variance in VC and correctly classified 76.0% of cases. Increasing age and higher PLR were associated with an increased likelihood of exhibiting VC (CAC or TAC), with *P* = 0.00 and 0.04, respectively.

There was a strong and positive correlation between CACS and age, which was statistically significant (*rs* = 0.495, *P* = 0.00). A positive correlation also existed between CACS and total cholesterol levels, which was statistically significant (*rs* = 0.269, *P* = 0.019) (Table 3).

A statistically significant positive correlation existed between TACS and age (*rs* = 0.516, *P* = 0.00). Similarly, a positive correlation was found between NLR, PLR, and TACS. (*rs* = 0.334, *P* = 0.001, and *rs* = 0.438, *P* = 0.00, respectively).

On multivariate linear regression analysis, increased age and RDW were found to be significant predictors of log(n) TACS (Table 4). However, none of the variables significantly predicted CACS in multivariate regression analysis.

NLR of 3.6 gave a sensitivity of 65% and a specificity of 45% for predicting the presence of coronary or thoracic aorta VC. Area under the curve for NLR was 0.671. PLR of 135 gave a sensitivity of 80% and a specificity of 50% for predicting the presence of coronary or thoracic aorta VC. Area under the curve for PLR was 0.705 (Figure 1). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of NLR and PLR for the presence of coronary/thoracic aortic VC at different cutoff values are detailed in Table 5.
Table 1. Demographic and laboratory features of the study groups.

|                          | Calcification absent (CAC/TAC), n = 50 mean±SD | Calcification present (CAC/TAC), n=40 mean±SD | P         |
|--------------------------|-----------------------------------------------|-----------------------------------------------|-----------|
| Age (years)              | 35.1±9.57                                     | 47.25±8.9                                     | <0.001    |
| BMI                      | 20.3±3.45                                     | 21.56±3.38                                    | 0.09      |
| Vintage (months)         | 18.4±13.79                                    | 14.43±10.69                                   | 0.14      |
| Sex*                     |                                               |                                               |           |
| Male                     | 31                                             | 27                                             |           |
| Female                   | 19                                             | 13                                             |           |
| Dialysis**               |                                               |                                               |           |
| HD                        | 46                                             | 37                                             |           |
| PD                        | 4                                              | 3                                              |           |
| Comorbidity**            |                                               |                                               |           |
| HTN                      | 41                                             | 29                                             | 0.27      |
| DM                       | 4                                              | 6                                              |           |
| CVA                      | 0                                              | 2                                              |           |
| Basic disease**          |                                               |                                               |           |
| DKD                      | 4                                              | 6                                              | 0.06      |
| HN                        | 12                                             | 20                                             |           |
| CIN                       | 5                                              | 3                                              |           |
| CGN                       | 25                                             | 7                                              |           |
| Unknown                   | 4                                              | 4                                              |           |
| Hemoglobin (g/dL)        | 8.84±2.35                                     | 9.54±2.35                                     | 0.16      |
| NLR                      | 3.54±1.25                                      | 4.51±1.65                                     | 0.002     |
| PLR                      | 144±57.51                                      | 196.48±79.13                                  | <0.001    |
| RDW (%)                  | 15.25±1.71                                     | 15.54±1.42                                    | 0.39      |
| MPV (fL)                 | 10.94±1.08                                     | 11.22±0.91                                    | 0.22      |
| Calcium (mg/dL)          | 8.58±0.68                                      | 8.37±0.48                                     | 0.11      |
| Phosphorus (mg/dL)       | 5.69±2.0                                       | 5.66±2.02                                     | 0.94      |
| Ca×P                     | 49.16±21.94                                    | 45.66±15.69                                   | 0.39      |
| iPTH (pg/mL)             | 255.99±301.48                                  | 270.62±271.47                                 | 0.81      |
| Vitamin D                | 15.42±11.19                                    | 16.54±13.71                                   | 0.67      |
| CACS                      | 149.38±231.33                                  | 0                                              | --        |
| TACS                      | 202.11±260.61                                  | 0                                              | --        |
| Uric acid (mg/dL)        | 6.17±2.48                                      | 6.5±1.34                                      | 0.49      |
| Total cholesterol (mg/dL)| 130.78±40.11                                   | 155.21±39.87                                  | 0.01      |
| Triglyceride (mg/dL)     | 127.67±74.17                                   | 139.36±11.87                                  | 0.62      |
| LDL (mg/dL)              | 79.94±27.95                                    | 90.04±32.66                                   | 0.19      |
| HDL (mg/dL)              | 40.06±9.07                                     | 45.33±10.36                                   | 0.23      |
| VLDL (mg/dL)             | 16.39±6.91                                     | 17.93±7.42                                    | 0.41      |

Independent samples t-test, *Chi-square test, **Fisher’s exact test used, P<0.05 is statistically significant

CAC: Coronary artery calcification, TAC: Thoracic aortic calcification, HTN: Hypertension, DM: Type 2 diabetes mellitus, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, RDW: Red cell distribution width, MPV: Mean platelet volume, iPTH: intact parathyroid hormone, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, DKD: Diabetic kidney disease, HN: Hypertensive nephropathy, CIN: Chronic interstitial nephritis, CGN: Chronic glomerulonephritis, TACS: Thoracic aortic calcification score.
Table 2. Predictors of the calcification.

| Variables | Univariate analysis | Multivariate analysis |
|-----------|---------------------|-----------------------|
|           | Odds ratio          | 95% CI                | P         | Adjusted odds ratio | 95% CI    | P         |
| Age (years) | 1.15                | 1.08–1.21             | <0.001    | 1.12                | 1.05–1.20 | <0.001    |
| PLR        | 1.01                | 1.00–1.02             | 0.020     | 1.02                | 1.01–1.03 | 0.040     |

Outcome variable: Calcification (present/absent), PLR: Platelet-to-lymphocyte ratio, CI: Confidence interval. Binary logistic regression analysis used. Variables (with \( P < 0.05 \)) in univariate analysis included in multivariate analysis, \( P < 0.05 \) is statistically significant.

Table 3. Spearman’s correlation analysis between the variables.

| Variables | CACS   | P     | TACS   | P     |
|-----------|--------|-------|--------|-------|
| Age       | 0.495  | <0.001| 0.516  | <0.001|
| NLR       | 0.186  | 0.079 | 0.334  | 0.001 |
| PLR       | 0.017  | 0.877 | 0.438  | 0.001 |
| Total cholesterol | 0.269 | 0.019 | 0.133  | 0.255 |

Outcome variable: CACS and TACS, \( P < 0.05 \) is statistically significant.

CAC: Coronary artery calcification, TAC: Thoracic aortic calcification, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, TACS: Thoracic aortic calcification score.

Table 4. Predictors of the thoracic aortic calcification score of the study patients using multiple linear regression analysis.

| Variables | Thoracic aortic calcification score |
|-----------|-------------------------------------|
|           | Simple (univariate) linear regression | Multiple linear regression |
|           | Unstandardized regression coefficient | Standard error | \( P \) | Unstandardized regression coefficient | Standard error | \( P \) |
| Constant  | -                                  | -               | -       | -5.240 | 2.873 | 0.080 |
| Age       | 0.068                              | 0.03            | 0.031   | 0.064 | 0.029 | 0.039 |
| RDW       | 0.537                              | 0.189           | 0.09    | 0.442 | 0.183 | 0.023 |

Outcome variable: TACS, \( R^2 = 0.298 \). In the above model, regression coefficient and constant were estimated after dependent variable underwent transformation to log normal value.

Linear regression analysis used. Variables (with \( P < 0.05 \)) in univariate analysis included in multivariate analysis, \( P < 0.05 \) is statistically significant. RDW: Red cell distribution width, TACS: Thoracic aortic calcification score.

Figure 1. ROC curve for NLR and PLR to predict vascular calcification.

ROC: Receiver operating characteristic, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.
In this study, we evaluated the relationship and predictive value of various blood cell parameters with coronary and thoracic aorta VC in dialysis-dependent ESRD population. There are multiple risk factors associated with VC such as age, uremia, elevated CRP, phosphorus levels, calcium × phosphorus product, diabetes mellitus, duration of dialysis, and hypertension. However, the relationship between VC and risk factors is far from being uniform.

Pro-inflammatory cytokines are known to suppress red blood cell (RBC) maturation, which leads to the release of immature RBCs getting reflected in high RDW. Similarly, higher MPV is related to increased production of pro-inflammatory active platelets. Prolonged stressful condition causes increased sympathetic stimulation, which leads to cortisol secretion. This results in a decrease in the relative concentration of lymphocytes. Earlier studies have shown an increased platelet counts in chronic inflammation. Similarly, NLR has also been shown to be an inflammatory marker in ESRD population. In the background of these findings, we studied these parameters and found that RDW and MPV do not correlate with either the presence/absence of VC or CACS/TACS. However, high PLR did predict the presence of VC. Both PLR and NLR correlated well with TACS. Considering the fact that TAC is a risk factor for future adverse cardiovascular events, PLR can be an effective screening tool to obtain evidence of TAC. TAC is usually more common than CAC as is also evident in our study. RDW was found to be a significant predictor of TACS in our study, which is somewhat similar to the study by Gürel et al, in which they have reported its association with CACS.

Increasing age has been persistently associated with VC and risk of cardiovascular death. The risk increases at least till the age of 65 years after which it diminishes. Our study mainly comprised of younger population, with the mean age of patients with VC being 47.25 ± 8.9 years. This puts this group into high cardiovascular risk category demanding good screening methods and aggressive medical management.

Our study demonstrated a very low prevalence of VC in population <30 years age. Of 21 patients aged <30 years of age, only three showed evidence of VC. This is substantially different from that reported by Goodman et al who showed 87% prevalence in 20–30 years age group in a similar population. Dialysis vintage could be one of the reasons behind the difference as the mean dialysis duration was 14 ± 5 years in their study compared to 1.5 ± 1 year in ours. Difference in the ethnicity of population can also be another factor behind it. Toussaint et al demonstrated a sensitivity and specificity for CT aortic VC ≥500 HU to 50% and 86%, respectively. In another study by Marinelli et al, the sensitivity and specificity

| Cutoff value | Sensitivity | Specificity | PPV | NPV |
|--------------|-------------|-------------|-----|-----|
| **NLR**      |             |             |     |     |
| 2.86         | 0.8         | 0.32        | 0.48| 0.67|
| 3.52         | 0.7         | 0.5         | 0.53| 0.68|
| 3.755        | 0.65        | 0.62        | 0.58| 0.69|
| 4.225        | 0.55        | 0.72        | 0.61| 0.67|
| **PLR**      |             |             |     |     |
| 93.215       | 0.925       | 0.22        | 0.49| 0.79|
| 103.25       | 0.9         | 0.3         | 0.51| 0.79|
| 135          | 0.8         | 0.5         | 0.56| 0.76|
| 162.805      | 0.6         | 0.76        | 0.67| 0.70|

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PPV: Positive predictive value, NPV: Negative predictive value.
of X-ray imaging compared to ultrasonography for the detection of arterial medial calcification on the superficial femoral artery were 47% and 100%, respectively. In our study, PLR of 135 had a good sensitivity of 80% to predict VC. It is clear that imaging gives a high specificity albeit lacks sensitivity. If we can use a combination of PLR with high sensitivity and X-ray with high specificity, we can predict VC to an acceptable clinical value.

Our study has a few limitations. There were no age-matched controls. The cross-sectional nature of the study disabled the incorporation of the variations in the various parameters that may occur in individuals over time. The strength of the study lies in focusing on the younger age group of study population, which is at a substantially higher risk of ischemic cardiovascular events.

Conclusion

The present study indicates that the components of the complete blood count, namely, NLR and PLR, which are reported in routine clinical practice, can be used to predict VC in ESRD patients. Higher age and RDW can be predictive of TACS. Being a cost-effective and easily available investigation, the utilization of their correlation with CAC and TAC appears promising, particularly in the age group of 30–60 years. This may prompt focus on anti-inflammatory treatment strategies and lower threshold for performing preventive cardiovascular screening procedures. Future large-scale studies are warranted to throw more light on these findings.

Acknowledgment

We thank Dr. Prabhaker Mishra, Assistant Professor, Department of Biostatistics and Health Informatics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, for assistance with statistics that helped improve the manuscript.

Conflict of interest: None declared.

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Date of manuscript receipt: 4 September 2018.
Date of revised copy receipt: 31 October 2018.
Date of final acceptance: 31 October 2018.