DOI: 10.4149/BLL_2022_084

Bratisl Med J 2022; 123 (7)
523–527

CLINICAL STUDY

Cardiac valve calcification prevalence and association with neutrophil-to-lymphocyte ratio in newly diagnosed patients with non-dialysis chronic kidney disease stage 3–5

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ABSTRACT
OBJECTIVE: Cardiac valvular calcification (CVC) is the main cause of cardiovascular disease and all-cause death in patients with chronic kidney disease (CKD). However, the relationship between Neutrophil lymphocyte ratio (NLR) and CVC in patients with CKD is not clear. In this study, we aimed to investigate the prevalence of CVC in newly diagnosed patients with non-dialysis CKD stage 3–5 and evaluate the correlation between NLR and CVC.
METHODS: A total of 483 newly diagnosed patients with non-dialysis CKD stage 3–5 were included. According to the presence of CVC, these patients were retrospectively divided into two groups: CVC group and non-CVC group.
RESULTS: CVC was found in 80 patients (16.56 %), 53 (10.97 %) of whom had only aortic valve calcification (AVC), 18 (3.73 %) had mitral valve calcification (MVC), and 9 (1.86 %) had both AVC and MVC. The level of NLR in the CVC group was significantly higher than that in the non-CVC group (p=0.002). Multivariate logistic regression analysis showed that NLR was an independent risk factor for CVC (95% CI 1.017~1.225, p=0.020). ROC curve analysis showed that the area under the curve of NLR for predicting CVC was 0.610 (95% CI 0.543–0.676, p=0.002). The best cut-off point of NLR was 3.340, with a sensitivity of 49.4 % and a specificity of 70.0 %.
CONCLUSION: CVC is not uncommon in newly diagnosed patients with non-dialysis CKD stage 3–5, and NLR is an independent risk factor for CVC *(Tab. 4, Fig. 1, Ref. 34)*. Text in PDF *www.elis.sk*
KEY WORDS: cardiac valvular calcification, chronic kidney disease, neutrophil-to-lymphocyte ratio, inflammation.

Introduction

Chronic kidney disease (CKD) has become a global public health problem that seriously threatens human health. According to statistics, the global prevalence rate of CKD is in a range from 11 % to 13 % (1). In China, the prevalence of CKD in people over 18 years old is 10.8 % (2). Cardiovascular disease is the leading cause of death in patients with CKD, and it is closely linked to CKD (3, 4). With the decrease in renal function, the incidence of cardiovascular disease increases gradually (5). Cardiac valvular calcification (CVC) is not only a high-risk factor for cardiovascular disease, but also an effective predictor of cardiovascular and all-cause death in patients with CKD (6, 7).

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Neutrophil lymphocyte ratio (NLR) is a parameter of whole blood cell count, which was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. More importantly, NLR is also a new cardiovascular disease marker (8). It has been shown that patients with CVC have higher NLR level, but patients with a history of CKD were excluded (9). To our knowledge, there are few published data on the relationship between the NLR and the presence of CVC in patients with CKD. Therefore, our study aims to explore the relationship between NLR and CVC by investigating the condition of CVC in newly diagnosed patients with non-dialysis CKD stage 3–5.

Materials and methods

We performed a retrospective study of newly diagnosed inpatients with non-dialysis CKD stage 3–5 who were examined by echocardiography at the Department of Nephropathy, People's Hospital of Leshan from February 2016 to June 2021. The eGFR was calculated using the CKD-Epidemiology Collaboration Equation (CKD-EPI) (10). Based on eGFR,

Tab. 1. CVC, AVC, and MVC with different stages of CKD.

Variable	Total	CKD stage 3	CKD stage 4	CKD stage 5	p
CVC (%)	80 (16.56)	11 (9.57)	21 (19.44)	48 (18.46)	0.067
Only AVC (%)	53 (10.97)	8 (6.96)	12 (11.11)	33 (12.69)	0.261
Only MVC (%)	18 (3.73)	1 (0.87)	6 (5.56)	11 (4.23)	0.149
Both AVC and MVC (%)	9 (1.86)	2 (1.74)	3 (2.77)	4 (1.54)	0.731

CVC – Cardiac valvular calcification, AVC – aortic valve calcification, MVC –mitral valve calcification

Tab. 2. Demographic and clinical characteristics of the study population.

Variable	CVC group (n=80)	Non-CVC group (n=403)	p
Age (years)	71.65±10.50	56.08±14.97	<0.001
Male (%)	44 (55.00)	223 (55.33)	0.956
History of Smoking (%)	16 (20.00)	123 (30.52)	0.058
Diabetes (%)	26 (32.50)	122 (30.27)	0.693
Hypertension (%)	58 (72.50)	207 (51.36)	<0.001
SBP (mmHg)	157.39±30.35	154.53±25.49	0.377
DBP (mmHg)	82.86±15.98	90.95±17.50	<0.001

SBP – Systolic blood pressure, DBP – Diastolic blood pressure

Tab. 3. Serological parameters of the study population.

Variable	CVC group (n=80)	Non-CVC group (n=403)	p
Erythrocytes ($\times 10^{12}$/L)	3.01±0.63	3.29±0.88	0.007
Hemoglobin (g/L)	88.65±19.36	96.48±26.07	0.011
Hematocrit (%)	27.91±5.80	30.23±7.84	0.012
Platelet ($\times 10^{9}$/L)	157.00 (119.75, 191.75)	162.00 (126.00, 208.00)	0.170
NLR	4.30 (2.75, 6.48)	3.38 (2.32, 5.05)	0.002
PLR	139.00 (95.00, 205.00)	124.00 (88.00, 173.00)	0.058
Serum albumin (g/L)	35.65 (32.70, 38.80)	36.30 (32.18, 39.73)	0.289
Blood urea (mmol/L)	18.36 (12.05, 29.00)	15.90 (10.62, 27.73)	0.195
Serum creatinine (umol/L)	364.90 (200.75, 669.25)	330.00 (182.00, 730.00)	0.884
Serum uric acid (umol/L)	492.00 (427.75, 575.50)	511.00 (428.00, 594.00)	0.242
eGFR (ml/min/1.73m²)	11.49 (5.65, 25.10)	14.01 (5.82, 31.22)	0.268
Serum hydrocarbonate (mmol/L)	18.63±4.50	19.45±4.72	0.155
Serum potassium (mmol/L)	4.54 (3.97, 5.00)	4.33 (3.91, 4.84)	0.092
Serum calcium (mmol/L)	2.09 (1.94, 2.18)	2.07 (1.90, 2.22)	0.748
Serum phosphorus (mmol/L)	1.39 (1.11, 1.78)	1.39 (1.16, 1.78)	0.463
TC (mmol/L)	4.40 (3.57, 5.44)	4.68 (3.79, 5.53)	0.173
TG (mmol/L)	1.39 (1.06, 2.02)	1.54 (1.17, 2.21)	0.114
HDL-C (mmol/L)	1.28 (1.06, 1.50)	1.29 (1.07, 1.55)	0.789
LDL-C (mmol/L)	2.07 (1.63, 2.71)	2.30 (1.84, 2.91)	0.020
AIP	2.38 (1.86, 3.08)	2.58 (1.98, 3.22)	0.421

SBP – Systolic blood pressure, DBP – Diastolic blood pressure, NLR – Neutrophil-to-lymphocyte ratio, PLR – Platelet-to-lymphocyte ratio, eGFR – estimated glomerular filtration rate, TC – Total cholesterol, TG – Triglyceride, HDL-C – High density lipoprotein cholesterol, LDL-C – Low density lipoprotein cholesterol, AIP – Atherogenic Index of Plasma.

the CKD staging criteria are as follows, CKD stage 3 (30–59 ml/min/1.73 m²), CKD stage 4 (15–29 ml/min/1.73 m²), CKD stage 5 (eGFR <15 ml/min/1.73 m²). Patients were excluded from the study if they were pregnant, lactating, or received renal replacement therapy such as renal transplantation or dialysis. In addition, patients who had a history of malignant tumors, hematological diseases such as multiple myeloma, or autoimmune diseases such as systemic lupus erythematosus, ANCA-associated vasculitis, and Sjogren's syndrome were excluded. Moreover, patients who received a blood transfusion in the past 4 months or were comorbid with active infection or gastrointestinal bleeding were also ruled out. According to the exclusion criteria, 483 cases were finally selected.

We collected data on patients' demographic and clinical features (age, sex, diabetes, hypertension, history of smoking, systolic and diastolic blood pressure), laboratory tests (complete blood counts, serum albumin, blood urea, serum creatinine, serum uric acid, serum hydrocarbonate, serum potassium, serum calcium, serum phosphorus, total cholesterol, triglyceride, high- lipoprotein cholesterol, low-density lipoprotein cholesterol, atherogenic index of plasma), and echocardiographic manifestation (CVC). NLR was calculated as the ratio of neutrophil count to lymphocyte count. PLR was calculated as the ratio of Platelet count to lymphocyte count. The study was approved by the Ethics Committee of Leshan People's Hospital (NO: 201908).

All statistical data and figure generation were performed with SPSS software vision 25.0 (SPSS Inc., Chicago, Illinois, USA) and GraphPad Prism software vision 7.0 (GraphPad Software Inc., San Diego, CA, USA). Continuous and normally distributed variables were expressed as mean ± standard deviation (SD) and analyzed using the independent sample t-test. Continuous and nonnormally distributed variables were expressed as median (interquartile range) and analyzed using the Mann-Whitney U test. Categorical variables were expressed as numbers and frequencies and analyzed using the chi-square test. Multivariable logistic regression analysis was employed to identify factors associated with CVC. Receiver operating characteristic (ROC) curve analysis was carried out to evaluate the predictive value of NLR to CVC. $p < 0.05$ was considered as the indication of significant differences.

Results

The prevalence of CVC, aortic valve calcification (AVC), and mitral valve calcification (MVC) with different stages of CKD are shown in Table 1. A total of 483 newly diagnosed patients with non-dialysis chronic kidney disease stage 3–5 were enrolled, and 80 (16.56 %) patients with CVC were detected, 53 (10.97 %) of whom had only AVC, 18 (3.73 %) had MVC, and 9 (1.86 %) had both AVC and MVC. However, there were no significant differences among different stages of CKD.

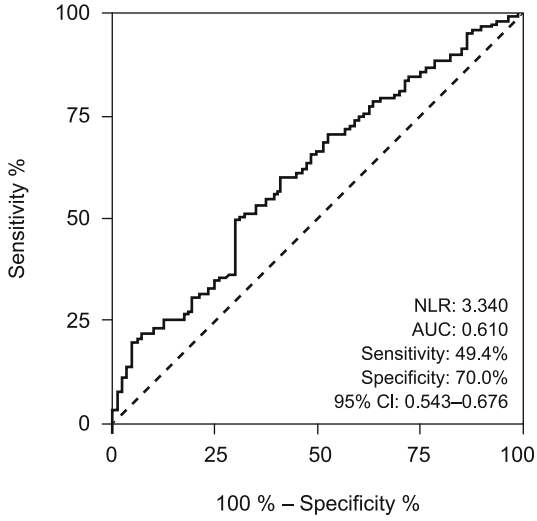

Fig. 1. ROC curve of NLR for predicting CVC.

The demographic and clinical characteristics of the study population are shown in Table 2. Patients in the CVC group were substantially older than those in the non-CVC group ($p < 0.001$). Besides, the proportion of hypertension in the CVC group was substantially higher than that in the non-CVC group ($p < 0.001$), but DBP in the CVC group was substantially lower than that in the non-CVC group ($p < 0.001$). However, there were no significant differences between the two groups concerning males, history of smoking, diabetes, and SBP.

Serological parameters of the study population are shown in Table 3. NLR in the CVC group was substantially higher than that of the non-CVC group, while erythrocytes, hemoglobin, hematocrit, and LDL-C in the CVC group were substantially lower than those in the non-CVC group (all $p < 0.05$). However, Platelet, PLR, serum albumin, blood urea, serum creatinine, serum uric acid, eGFR, serum hydrocarbonate, serum potassium, serum calcium, serum phosphorus, TC, TG, HDL-C, and AIP did not differ significantly between the two groups.

The variables with statistical differences in Tables 2 and 3 were included in multivariate logistic regression analysis. The results showed that history of hypertension (OR 2.106, 95% CI 1.149~3.859), higher age (OR 1.095, 95% CI 1.068~1.122), higher NLR (OR 1.116, 95% CI 1.017~1.225) and lower hematocrit (OR 0.946, 95% CI 0.906~0.988) were independent risk factors of CVC (Tab. 4).

Tab. 4. Multivariate logistic regression analysis for CVC.

Variable	β	Standard error	Wald	OR (95%CI)	p
Age	0.091	0.013	52.243	1.095 (1.068~1.122)	<0.001
Hypertension	0.745	0.309	5.808	2.106 (1.149~3.859)	0.016
Hematocrit	–0.055	0.022	6.162	0.946 (0.906~0.988)	0.013
NLR	0.110	0.047	5.398	1.116 (1.017~1.225)	0.020

NLR – Neutrophil-to-lymphocyte ratio, OR – Odds ratio, CI – Confidence interval.

ROC curve analysis was performed to measure the predictive value for CVC of NLR. The area under the curve (AUC) was 0.610 for the presence of CVC ($p = 0.002$). A cut-off value of 3.340 for NLR had a sensitivity and specificity of 49.4 % and 70.0 %, respectively, for the presence of CVC (Fig. 1).

Discussion

Cardio-cerebrovascular events such as cardiac valvular stenosis, arrhythmia, heart failure, myocardial infarction, and stroke are connected to CVC, posing a significant hazard to human health (11–13). Echocardiography is a critical tool for evaluating heart structure and function since it is accurate, dependable, non-invasive, and convenient. According to the KDIGO guidelines, CVC should be evaluated using echocardiography (14). Unfortunately, CVC has received far greater attention in patients with dialysis CKD (15, 16). In the present study, we utilized echocardiography to evaluate CVC in newly diagnosed patients with non-dialysis CKD stage 3–5. We found that about one-sixth of patients had CVC. Similarly, another Chinese single-center study showed that 20.4 % of patients with non-dialysis CKD had CVC (17). By contrast, studies in Russia and Finland revealed that the prevalence of CVC in patients with non-dialysis CKD was 27.3 % and 31 %, respectively (18, 19). We also discovered that the prevalence of AVC was higher than that of MVC, which corresponded to Hensen's previous study (20).

NLR is a compound biomarker that can be obtained by blood routine examination. It is inexpensive and does not place an additional medical burden on patients. Moreover, NLR is more stable than other single leukocyte parameters, which are easily affected by dehydration, blood sample dilution, and treatment. Zahorec observed a significant increase in neutrophil count and a significant decrease in lymphocyte count in patients with tumors complicated with severe infection, and he proposed that NLR may be used as a simple parameter to evaluate the degree of inflammation for the first time (21). In recent years, more and more studies have demonstrated that NLR is a new type of inflammatory marker (22, 23). It was reported that NLR also played a major role in the identification of inflammation in patients with CKD (24, 25).

Vascular calcification includes calcified atherosclerotic plaque, arterial calcification, CVC, and calcification prevention (26). Arterial calcification can lead to vascular stenosis and reduced blood flow, resulting in angina pectoris, myocardial infarction, and stroke. CVC can worsen heart failure by causing valvular regurgitation, stenosis, and dysfunction. For a long time, vascular calcification was considered as a degenerative change with age. It is now widely believed to be a chronic inflammatory lesion, which involves a variety of inflammatory cells, inflammatory cytokines, adhesion molecules, and chemokines (27, 28). It could be the potential physiological mechanism for the association of NLR with CVC from the standpoint of inflammation. Elevated NLR, on the other hand, indicates a rela-

tive increase in neutrophil count, which releases matrix metalloproteinases that contribute to CVC (29). A previous study found that NLR level in CKD patients with arterial calcification was significantly higher than in those without arterial calcification (30). In another study, Chandra et al. showed that NLR level was positively correlated with artery calcification score (31). As another common type of vascular calcification, the results of Varol et al showed that NLR was significantly increased in patients with CVC (9). Avci et al pointed out that the degree of NLR elevation was related to the severity of calcific aortic stenosis (32). However, none of their studies included patients with CKD (9, 32).

In order to explore the relationship between NLR and CVC in newly diagnosed patients with non-dialysis CKD stage 3 – 5, we compared the difference of NLR between the CVC group and the non-CVC group. The result showed that the level of NLR in the former was significantly higher, indicating that elevated NLR may reflect CVC in these patients. Besides, multivariate logistic regression analysis showed that elevated NLR was an independent risk factor for CVC, and further ROC curve showed that the AUC for predicting CVC by NLR was 0.610. When the optimal critical value was 3.340, its sensitivity and specificity were 49.4 % and 70.0 %, respectively. Based on the findings of this study, we hypothesized that NLR could be an effective marker for predicting CVC in newly diagnosed patients with non-dialysis CKD stage 3 – 5.

It is widely believed that aging is a traditional risk factor for CVC. The present study also showed that CVC was closely related to age. Hypertension was independently associated with CVC in a related study (33). Our findings backed up this assertion. We also discovered that erythrocytes, hemoglobin, and hematocrit in the CVC group were significantly lower than those in the non-CVC group, and reduced hematocrit was an independent risk factor for CVC. The above indexes are laboratory parameters that reflect anemia. Anemia leads to hemodynamic imbalance, which increases mechanical stimulation of heart valve. Mechanical stimulation changes the microenvironment of heart valve and promotes CVC (34).

Conclusions

Our results suggest that CVC was common in newly diagnosed patients with non-dialysis CKD stage 3-5. NLR was a significant independent predictor of CVC in this population. Further researches are needed to determine the optimal critical value of NLR to predict CVC.

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Received February 1, 2022.
Accepted February 21, 2022.