Article

CHA2DS2-VASc Score, Fibrinogen, and Neutrophil to Lymphocyte Ratio as Predictors of In-Stent Restenosis in Patients with Severe Kidney Disease

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Abstract

Objective: This study examined the relationship between CHA2DS2-VASc score, fibrinogen (FIB), and neutrophil-to-lymphocyte ratio (NLR) with in-stent restenosis (ISR) in patients with severe kidney disease (SKD). Methods: Between January 2017 and January 2022, patients with SKD who underwent coronary stent implantation at the Second Hospital of Tianjin Medical University were retrospectively analyzed. According to whether ISR occurred within 2 years of postoperative follow-up, 164 patients were categorized into the ISR group (n = 62) and the non-ISR group (n = 102). According to the Modification of Diet in Renal Disease (MDRD) formula, SKD is defined as an estimated glomerular filtration rate (eGFR) less than 30 mL/(min·1.73 m²). Angiographic ISR was defined as a stented coronary artery segment with more than 50% constriction during the follow-up angiography. Relevant clinical data and laboratory parameters were obtained from the hospital’s medical records. Results: In total, 164 patients were included (mean age: 67.1 [10.2] years, 65.2% men), grouped into 62 patients with ISR and 102 patients without. A significant difference was found in the age, previous strokes, congestive heart failure (CHF), NLR, platelet-to-lymphocyte ratio (PLR), fibrinogen, CHA2DS2-VASc score, and risk classification of CHA2DS2-VASc score of patients in the ISR group as compared to those in the non-ISR group. In a multivariable logistic regression analysis, the CHA2DS2-VASc score, fibrinogen, and NLR were identified as independent predictors of ISR. The analysis of the receiver operating characteristic (ROC) curve revealed that the area under the curve (AUC) value was 0.714 (95% confidence interval (CI): 0.634–0.793) for the CHA2DS2-VASc score and 0.652 (95% CI: 0.565–0.739) for FIB, 0.707 (95% CI: 0.627–0.788) for NLR, and 0.797 (95% CI: 0.725–0.868) for the combination of CHA2DS2-VASc score, FIB and NLR. Conclusions: The combination of CHA2DS2-VASc score, FIB, and NLR can more accurately predict the occurrence of ISR in SKD patients.

Keywords

CHA2DS2-VASc score; fibrinogen; NLR; ISR; severe kidney disease

Introduction

Interventional cardiologists still encounter challenges associated with in-stent restenosis (ISR), despite advancements in materials, techniques, and medications. Clinical, procedural, and stent-related factors influence the incidence of ISR, which ranges from 20.0% to 50.3% [1]. An estimated glomerular filtration rate (eGFR) less than 30 mL/(min·1.73 m²), with or without preexisting dialysis, is considered severe kidney disease (SKD) [2]. A systemic, chronic proinflammatory state is caused by chronic renal disease (CKD), contributing to calcification of cardiac valves, myocardial fibrosis, atherosclerotic lesions, as well as vascular calcification and vascular senescence. A study indicates that patients with chronic kidney disease (CKD), particularly those with end-stage kidney disease, are more susceptible to ISR [3]. However, previous research on coronary restenosis in stents has not included patients with SKD.

The CHA2DS2-VASc score is utilized to assess the risk of embolism in patients with atrial fibrillation (AF) based on congestive heart failure (CHF), hypertension, diabetes mellitus, stroke history, vascular disease, and female gender [4]. Recently, several studies have proved that the CHA2DS2-VASc score is predictive of ISR in various patient populations [2,5–7]. Underexpansion or fracture are the primary mechanical factors leading to stent failure, while local inflammation, aggressive neointimal proliferation, late acquired malposition, or neoatherosclerosis are the main biological factors [8]. It is well established that inflammation and neointima formation are the primary mechanisms of ISR [9]. In recent years, fibrinogen (FIB) and neutrophil-to-lymphocyte ratio (NLR) have been identified as new inflammatory markers. This study aims to analyze...
the prognostic significance of the combined CHA2DS2-VASc score with FIB and NLR for the occurrence of ISR in individuals with SKD prior to undergoing percutaneous coronary intervention (PCI).

Materials and Methods

Study Population

In this retrospective analysis, individuals diagnosed with SKD who received effective stent placement from January 2017 to January 2022 were examined. One hundred and sixty-four patients were divided into two groups: the ISR group (n = 62) and the non-ISR group (n = 102), based on whether ISR occurred within 2 years of postoperative follow-up. Coronary angiograms were independently interpreted by two cardiologists who were blinded to the study. Angiographic ISR was defined as \( >50\% \) stenosis in the coronary artery segment where the stent was placed during follow-up angiography. According to the Modification of Diet in Renal Disease (MDRD) formula, SKD is defined as an eGFR less than 30 mL/(min\( \cdot \)1.73 m\(^2\)), with or without dialysis. The following information, including gender, age, smoking habits, hypercholesterolemia, hypertension, diabetes mellitus, history of stroke, and laboratory results, was extracted from medical records.

Patients who underwent successful stent implantation between 2017 and 2022 and had an eGFR of <30 mL/(min\( \cdot \)1.73 m\(^2\)) were enrolled. If they refused or abandoned treatment, did not report for the control visit, or suffered from autoimmune disease, blood system disease, serious lung, liver, tumor, or other underlying diseases, or cachexia, they were not eligible for enrollment.

Clinical Characteristics

Based on the CHA2DS2-VASc scoring system, individuals with CHF, women, age 65–74 years, hypertension, diabetes mellitus, and vascular disease were assigned 1 while those aged \( \geq 75 \) years and with a history of stroke or transient ischemic attack were assigned 2 points [3]. Patients with left ventricular ejection fraction (LVEF) below 40% and presenting clinical symptoms or chest X-ray findings indicative of congestion were categorized as having CHF. Patients with a systolic blood pressure greater than 140 mm Hg and/or a diastolic blood pressure greater than 90 mm Hg in two separate measurements or while on continuous antihypertensive treatment were defined as hypertensive. Patients were determined to have diabetes mellitus if they adhered to a diabetic diet, were using antidiabetic medication, or had a fasting venous glucose level exceeding 126 mg/dL on two separate occasions. The diagnosis of hypercholesterolemia relied on the identification of a total cholesterol level of \( \geq 200 \) mg/dL in the fasting state. Based
on the echocardiographic and demographic profiles of individual patients, CHA2DS2-VASc scores were calculated before PCI. All patients had a minimum score of 1 following PCI. The eGFR was calculated using the MDRD [10].

### Statistical Analysis

SPSS (version 26.0 for Mac, SPSS, Inc., Chicago, IL, USA) was used to analyze the data. Continuous variables were represented as mean (standard deviation) or median (interquartile range), and categorical variables were displayed as percentages and counts. The Student’s t-test or the Mann-Whitney U test was used to compare continuous variables, while the χ² test or Fisher’s exact test was used to compare categorical variables. Simple logistic regression analysis was conducted to examine the relationship between the variables and ISR, while multivariate logistic regression analysis was performed to evaluate variables with a significance level of \( p < 0.10 \). The study employed the adjusted odds ratio (OR) and a 95% confidence interval (CI) to present the findings of the regression analysis. The predictive capacity of the CHA2DS2-VASc score, FIB, and NLR for ISR was assessed through ROC curve analyses. Statistical significance was defined as a two-sided \( p \) value of less than 0.05.

### Results

Based on the presence of ISR, a total of 164 individuals (mean age: 67.1 \([10.2]\) years, 65.2% men) were categorized into two groups, with 62 patients exhibiting ISR. The baseline characteristics of the study population are presented in Table 1. In comparison to the non-ISR group, patients in the ISR group were of advanced age, had a higher incidence of previous stroke and CHF, and a lower LVEF. There were no significant differences in the prevalence of hypertension, diabetes, and hyperlipidemia between the two groups. However, the prevalence of hyperlipidemia was observed to be higher in the ISR group as opposed to the non-ISR group.

The laboratory parameters are listed in Table 2. In comparison to the non-ISR group, the NLR, platelet-to-lymphocyte ratio (PLR), and FIB exhibited significantly elevated levels in the ISR group. The evaluation results of the CHA2DS2-VASc score are presented in Table 3. The mean score (5.45 \([1.28]\) vs. 4.35 \([1.37]\), \( p < 0.001 \) and risk classification were notably higher in the ISR group. The incidence of ISR increased as the CHA2DS2-VASc score values increased (Fig. 1).
Table 2. Laboratory findings.

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>Non-ISR group (n = 102)</th>
<th>ISR group (n = 62)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLR</td>
<td>4.06 ± 3.16</td>
<td>6.58 ± 5.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLR</td>
<td>178.65 ± 111.59</td>
<td>214.62 ± 99.22</td>
<td>0.039</td>
</tr>
<tr>
<td>MLR</td>
<td>0.38 ± 0.25</td>
<td>0.46 ± 0.27</td>
<td>0.065</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>117.32 ± 23.07</td>
<td>114.71 ± 21.16</td>
<td>0.469</td>
</tr>
<tr>
<td>FIB</td>
<td>3.53 ± 1.26</td>
<td>4.11 ± 1.34</td>
<td>0.007</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>7.97 ± 3.39</td>
<td>9.10 ± 3.92</td>
<td>0.055</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>6.93 ± 1.30</td>
<td>7.03 ± 1.28</td>
<td>0.742</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.76 ± 1.61</td>
<td>4.65 ± 1.64</td>
<td>0.662</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.71 ± 0.92</td>
<td>1.96 ± 1.01</td>
<td>0.102</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.09 ± 0.60</td>
<td>0.93 ± 0.26</td>
<td>0.050</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.73 ± 1.02</td>
<td>2.97 ± 1.11</td>
<td>0.167</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>52.50 ± 15.15</td>
<td>51.23 ± 14.67</td>
<td>0.601</td>
</tr>
<tr>
<td>Globulin, g/L</td>
<td>30.92 ± 8.92</td>
<td>30.81 ± 6.05</td>
<td>0.938</td>
</tr>
</tbody>
</table>

Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; FIB, fibrinogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3. CHA2DS2-VASc score and evaluation results.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-ISR group (n = 102)</th>
<th>ISR group (n = 62)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA2DS2-VASc score</td>
<td>3.85 ± 1.28</td>
<td>4.87 ± 1.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low risk (0–1 score)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Medium risk (2–3 score)</td>
<td>37 (36.3%)</td>
<td>10 (16.1%)</td>
<td></td>
</tr>
<tr>
<td>High risk (≥4 score)</td>
<td>64 (62.7%)</td>
<td>52 (83.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke, vascular disease, age 65 to 74 years, female gender.

The significant predictors of ISR were identified using logistic regression (Table 4). Univariate analysis showed that age, prior stroke, CHF, LVEF, FIB, NLR, CHA2DS2-VASc score, and CHA2DS2-VASc score risk were significant predictors. Multivariable regression analysis revealed that FIB, NLR, and CHA2DS2-VASc score were independent predictors. ROC curve analysis showed that the AUC value was 0.714 (95% CI: 0.634–0.793) for CHA2DS2-VASc score, 0.652 (95% CI: 0.565–0.739) for FIB, 0.707 (95% CI: 0.627–0.788) for NLR and 0.797 (95% CI: 0.725–0.868) for CHA2DS2-VASc score combined with FIB and NLR (Table 5 and Fig. 2).

Discussion

Our study highlights that the CHA2DS2-VASc score, FIB and NLR are independent predictors of increased risk for ISR in SKD patients. Compared to other available risk stratification tools for ISR, the combination of these factors provides a reliable and easily applicable predictor in clinical practice for ISR in SKD patients.

The most frequently utilized method for PCI is the insertion of a stent, which is associated with potential complications including stent thrombosis and restenosis [5]. As PCI procedures become more complex and involve multiple vessels, ISR is becoming more prevalent. It is associated with various lesions, procedural elements, and clinical aspects, as well as, significantly, patient-specific factors. The demographics include age, female gender, hypertension, diabetes, CHF, renal failure, and stroke or transient ischemic attack (TIA). The mechanisms of ISR are complex. Inflammation and neo-intimal formation are crucial in revascularization [11]. Hypertension, diabetes mellitus, and hyperlipidemia are linked to heightened inflammation [12].

Research shows that patients with CKD have an increased risk of cardiovascular events, with 50% of CKD stage 4 to 5 patients experiencing cardiovascular disease (CVD) [13]. CVD risk factors associated with CKD encompass both conventional elements such as hypertension and diabetes, and non-conventional factors such as mineral and bone abnormalities, inflammation, oxidative stress, and anemia. Additionally, dialysis-related factors such as the type and frequency of dialysis and dialysate composition are linked to cardiovascular abnormalities in CKD. Conventional risk factors associated with coronary artery disease (CAD) are correlated with atherosclerosis in the early stages of CKD, whereas non-conventional risk factors become increasingly significant as glomerular filtration rate (GFR) declines, ultimately contributing to the formation of fibrocalcific lesions.
Calcification of the coronary arteries is common in CKD patients, with faster progression as kidney function GFR declines [14]. The progression of coronary calcification accelerates as CKD worsens [15]. Calcification of central arterial vessels increases cardiac afterload [16], leading to continuous left ventricular overload subsequently causes maladaptive changes and cardiomyocyte death. This, in turn, results in eccentric hypertrophy, followed by left ventricular dilatation, systolic dysfunction, and reduced ejection fraction [17]. Consistent with this, the study found a significant reduction in LVEF and CHF prevalence in the ISR group.

Hypertriglyceridemia and low levels of high-density lipoprotein (HDL) cholesterol, while most have normal levels of LDL cholesterol. The development of CAD in CKD patients is linked to changes in lipoproteins (such as LDL carboxymylation and HDL dysfunction). Risk factors for vascular calcification include aging, inflammation, mechanical stressors (such as shear stress and elastin fatigue), and the possible buildup of microbiome-dependent metabolites (e.g., trimethylamine N-oxide) [16]. The precise mechanism of uremic calcific small arteriopathy is not yet understood. It was previously believed that elevated levels of calcium and phosphorus caused calcification, resulting in uremic calcific small arteriopathy [17]. However, it has been discovered that calcification is a result of active cellular processes triggered by increased calcium and phosphorus concentrations, rather than just passive mineralization [18]. Furthermore, electrolyte imbalances are common in patients with CKD [19] and are associated with a poor prognosis [20]. Serum magnesium levels are often decreased in CKD patients, and magnesium has been found to interfere with the formation of hydroxyapatite crystals, potentially preventing vascular calcification in advanced CKD [21]. In this study, patients in the ISR group, as compared to the non-ISR group, were older and had a higher incidence of prior stroke.

Inflammation plays a crucial role in the pathophysiological process of CKD, which is considered a systemic inflammatory disease with multiple causes [22,23]. Research indicates that CKD patients exhibit more severe coronary plaque inflammation compared to non-CKD patients [24]. There is a progressive increase in proinflammatory circulating mediators as kidney function declines [25]. Proinflammatory processes in CKD patients encompass insulin resistance, oxidative stress due to advanced glycation end product accumulation, metabolic acidosis, reduced cytokine clearance, various infections such as periodontal disease, post-translational modification of blood carrier molecules, and epigenetic factors [22]. Inflammation acting on neoplastic endothelial tissue at the site of coronary stent implantation plays a key role in the progression of ISR.
Table 4. Factors associated with the incidence of ISR in both univariate and multivariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>p</td>
<td>OR</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td>Age/years</td>
<td>1.042</td>
<td>1.008–1.078</td>
<td>0.016</td>
<td>1.034</td>
<td>0.980–1.090</td>
<td>0.221</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>2.250</td>
<td>1.045–4.842</td>
<td>0.038</td>
<td>0.989</td>
<td>0.285–3.433</td>
<td>0.987</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2.866</td>
<td>1.259–6.523</td>
<td>0.012</td>
<td>0.444</td>
<td>0.088–2.247</td>
<td>0.327</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.963</td>
<td>0.936–0.992</td>
<td>0.011</td>
<td>0.990</td>
<td>0.941–1.041</td>
<td>0.686</td>
</tr>
<tr>
<td>FIB</td>
<td>1.412</td>
<td>1.084–1.838</td>
<td>0.010</td>
<td>1.407</td>
<td>1.007–1.967</td>
<td>0.045</td>
</tr>
<tr>
<td>NLR</td>
<td>1.198</td>
<td>1.075–1.335</td>
<td>0.001</td>
<td>1.221</td>
<td>1.022–1.459</td>
<td>0.028</td>
</tr>
<tr>
<td>PLR</td>
<td>1.003</td>
<td>1.000–1.006</td>
<td>0.051</td>
<td>0.997</td>
<td>0.992–1.002</td>
<td>0.276</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>1.888</td>
<td>1.423–2.504</td>
<td>&lt;0.001</td>
<td>2.111</td>
<td>1.207–3.691</td>
<td>0.009</td>
</tr>
<tr>
<td>CHA2DS2-VASc risk score</td>
<td>5.486</td>
<td>1.822–16.525</td>
<td>0.002</td>
<td>1.563</td>
<td>0.256–9.549</td>
<td>0.628</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; LVEF, left ventricular ejection fraction; NLR, neutrophil to lymphocyte ratio.

Table 5. Analyses of ROC curves.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>AUC</th>
<th>Maximum entry index</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA2DS2-VASc score</td>
<td>0.714</td>
<td>0.354</td>
<td>83.9%</td>
<td>51.5%</td>
<td>0.634–0.793</td>
</tr>
<tr>
<td>NLR</td>
<td>0.707</td>
<td>0.334</td>
<td>71.0%</td>
<td>62.4%</td>
<td>0.627–0.788</td>
</tr>
<tr>
<td>FIB</td>
<td>0.652</td>
<td>0.300</td>
<td>72.6%</td>
<td>57.4%</td>
<td>0.565–0.739</td>
</tr>
<tr>
<td>CHA2DS2-VASc score combined with FIB and NLR</td>
<td>0.797</td>
<td>0.539</td>
<td>80.6%</td>
<td>73.3%</td>
<td>0.725–0.868</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NLR, neutrophil to lymphocyte ratio.

FIB and NLR are novel prognostic and inflammatory markers in patients with cardiovascular disease. This investigation revealed that the levels of NLR and FIB were notably elevated in the ISR group compared to the non-ISR group. Both FIB and NLR were identified as independent risk factors for ISR in SKD.

The CHA2DS2-VASc score, originally designed for patients with AF, effectively integrates common CKD risk factors, making it a suitable predictor for ISR risk in this population. A higher CHA2DS2-VASc score indicates a greater number of CKD risk factors and an increased susceptibility to ISR. In recent years, numerous studies have demonstrated that the CHA2DS2-VASc score has predictive value for ISR in various patient populations [2,5–7]. Consistently, this research found that the CHA2DS2-VASc score was an independent risk factor for ISR in patients with SKD. The AUC of the CHA2DS2-VASc score was 0.714 (95% CI: 0.634–0.793), with a sensitivity of 83.9% and a specificity of 51.1%.

The study had several limitations. Firstly, it was a single-center, retrospective observational study with a limited sample size, potentially affecting the representativeness of the entire population with the condition. Secondly, the definition of ISR relied on subjective visual assessment by interventional cardiologists rather than more objective measures such as intravascular ultrasound or optical computed tomography. Thirdly, individual demographic characteristics, comorbidities, and medication use of each patient could have influenced the occurrence of ISR. Lastly, the study did not exclude patients with acute inflammatory conditions, which may have affected certain biomarkers.

Conclusions

The combination of CHA2DS2-VASc score, FIB, and NLR can more accurately predict the occurrence of ISR in SKD patients. Further prospective studies are needed to validate these findings.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

YS collected data, created the database and wrote the manuscript. BT analysed data, draw figures and tables, and modified manuscript. JC, KC, YX, QS and ZZ interpreted data and revised the manuscript critically for important intellectual content. QS provided funding support. GL, TL and XZ developed the study concept and design. All authors approved the final version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.
The study has been granted an exemption from requiring written informed consent by medical ethics committee of the second hospital of Tianjin Medical University. And this study protocol was reviewed and approved by medical ethics committee of the second hospital of Tianjin Medical University, approval number KY2023K161.

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Conflict of Interest

The authors declares no conflict of interest. TL serves as editorial board member of this journal. TL declares that he was not involved in the processing of this article and has no access to information regarding its processing.

References


