Predictive value of neutrophil-to-lymphocyte ratio on drug eluting stent restenosis in patients with type 2 diabetes mellitus

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Despite major advances achieved in percutaneous coronary intervention (PCI) and antithrombotic therapies, in-stent restenosis (ISR) is still a challenging clinical problem after PCI. It is very important to identify a new parameter for ISR risk stratification and as potential pharmacological targets. We previously reviewed that Neutrophil-to-lymphocyte ratio (NLR) may be the best predictor of ISR among several parameters of blood cells. Type 2 diabetes mellitus (T2DM) is closely related to inflammation and acts as an independent risk factor of ISR. However, few studies have evaluated the predictive role of the dynamic changes of NLR on ISR in patients with T2DM. Therefore, we aimed to analyze pre-procedural NLR value in the first PCI and the second coronary angiography (CAG), and evaluate its predictive value on ISR in patients with T2DM.

Drug-eluting stents (DES) designed in a way that inflammatory reactions to vessel wall injury and stent struts are attenuated by an anti-proliferative drug coating, have dramatically reduced the incidence of ISR, but this remains at 5% to 10% during the follow-up period.[1] ISR is defined as a stenosis diameter of >50% occurring in the segment inside the stent or 5 mm proximal or distal to the stent at follow-up angiography. Recent studies have highlighted several new combined or derived parameters related to blood cells that independently predict the risk of DES-ISR. NLR, identified as an effective inflammatory parameter, has been proven to be an independent predictor of ISR occurrence. The value of NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Consecutive patients between January 2016 and January 2019 with T2DM who underwent elective PCI with DES and follow-up angiography were retrospectively screened. The inclusion criteria were as follows: age of 45 to 80 years, diagnosis of angina pectoris (stable or unstable) and T2DM,

follow-up angiography within 6 to 15 months. Following patients were excluded: myocardial infarction within 2 months before stenting implantation, systemic diseases, and on treatments potentially affecting blood cell parameters including acute/chronic infectious or inflammatory disease, chronic kidney disease. All patients received successful DES implantation according to standard guidelines, and received aspirin (100 mg/day) and clopidogrel (300 mg loading dose, followed by 75 mg/day for at least 12 months). The predictive value of NLR in DES-ISR was tested using receiver operating characteristic (ROC) analysis. All probability values were two-sided, and $P < 0.05$ was considered statistically significant. All analyses were performed with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). As a retrospective study and data analysis was performed anonymously, this study was exempt from the ethical approval and informed consent from patients.

This study enrolled 96 patients with T2DM (mean age: 65.3 ± 8.4 years; 70.8% men) who were divided into two groups according to the second CAG result: ISR group ($n = 32$), non-ISR group ($n = 64$). The mean follow-up period for all patients between the first PCI and the second CAG was 11.0 ± 2.2 months. There were no significant differences in the distribution of cardiovascular risk factors, demographic data, comorbidities, medications, and angiographic characteristics between the two groups.

Patients in the ISR group had higher mean levels of NLR than non-ISR group in the first PCI (3.08 ± 1.17 *vs.* 2.31 ± 0.91, $P = 0.001$) and in the second CAG (3.16 ± 0.92 *vs.* 2.26 ± 0.66, $P < 0.001$). Although pre-procedural NLR values in the ISR group were higher than non-ISR group, there were no significant differences in NLR level between first PCI and the second CAG in two groups respectively. In multivariate logistic regression analysis to determine the predictors of ISR, only pre-procedural NLR
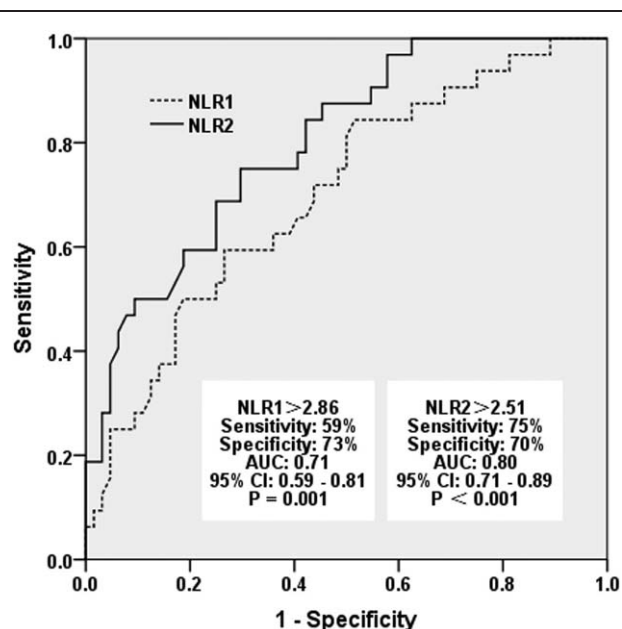
Figure 1: The comparisons of the ROC curves of the NLR1 and NLR2 for prediction of the in-stent restenosis. AUC: Area under the curve; CI: Confidence interval; NLR1: The first pre-procedural neutrophil-to-lymphocyte ratio; NLR2: The second pre-procedural neutrophil-to-lymphocyte ratio; ROC: Receiver operating characteristic.

was an independent risk predictor for DES-ISR in patients with T2DM.

As shown in Figure 1, ROC curves showed that the first pre-procedural NLR (NLR1) cutoff value for predicting ISR rate was 2.86 with a sensitivity of 59% and a specificity of 73% (area under the curve [AUC] = 0.71; 95% confidence interval [CI]: 0.59–0.81; $P = 0.001$); the second pre-procedural NLR (NLR2) cutoff value for predicting ISR rate was 2.51 with 75% sensitivity and 70% specificity (AUC = 0.80; 95% CI: 0.71–0.89, $P < 0.001$). The pairwise comparison of ROC curve analysis indicated that the difference between areas of the NLR1 and NLR2 for prediction of ISR was 0.098 (95% CI: 0.016–0.212, $P = 0.090$).

In the present study, we demonstrated that NLR was a powerful and independent predictor of ISR in patients with T2DM after successful DES implantation. According to ROC curves, we observed that the second pre-procedural NLR maybe better than the first in predicting ISR. Li et al[2] retrospectively studied 416 patients with coronary chronic total occlusion lesions and demonstrated that pre-procedural NLR before PCI is an independent risk factors for the development of ISR. Gabbasov et al[3] also conducted a study comprised of 126 patients with T2DM and concluded that NLR is an independent predictor for DES-ISR. Unfortunately, they ignored the pre-procedural NLR of the second CAG to predict ISR. We have previously reviewed that several parameters of blood cells, including the NLR, platelet-to-lymphocyte ratio (PLR), red blood cell distribution width (RDW), mean platelet volume (MPV),

and platelet distribution width (PDW),[4] can be used as risk predictors for DES-ISR in different clinical settings, while NLR may be the best predictor of DES-ISR among them.[5] However, our study showed that there were no significant differences in pre-procedural levels of PLR, RDW, MPV, and PDW between ISR group and non-ISR group. Different study populations and small number of samples may explain this discrepancy.

This study had several following limitations: First, it is a retrospective, non-randomized, single-center designed study. Due to the rigorous screening of the study population, the sample size is small, and large-scale prospective clinical studies are needed to confirm the conclusions. Second, the definition of stenosis is based on visual assessment rather than quantitative measurement, which may lead to an underestimation of the number of ISR cases. Third, it is necessary to further study the impact of diabetes course, location and complexity of coronary lesions, and the specific stent model on ISR.

In conclusion, the present study suggests that NLR, as a new marker of inflammation, is an independent risk factor for ISR in patients with T2DM after DES implantation, and the second pre-procedural NLR may have a better predictive value than the first in identifying DES-ISR. Therefore, NLR (baseline and follow-up value) deserves further study as reliable and easily available predictors of ISR to assist clinicians to stratify the risk of coronary angiographic and clinical outcomes related to DES-ISR in patients with T2DM.

Conflicts of interest

None.

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