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A Retrospective Analysis of Hematologic Parameters in Patients with Early Diabetic Kidney Disease

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Abstract

Objective: To retrospectively analyze the hematologic parameters in patients with early Diabetic Kidney Disease (DKD) to define potential biomarkers that can be used to predict early DKD.

Methods: 134 diabetic patients without nephropathy and 49 patients with early DKD were enrolled for this study and the hematologic parameters were retrospectively analyzed. Paired comparison was conducted by T-test and the predicting value of any statistically different parameter was tested using the Receiver Operating Characteristic curve (ROC) analysis model.

Results: The number of Neutrophil (N) was higher (P <0.001) while monocyte (M) was lower (P <0.01) in the early DKD group than that of DM group without nephropathy. In addition, neutrophil to lymphocyte ratio (NLR) was higher while platelet to lymphocyte ratio (PLR) was significantly lower in the early DKD group(P <0.001). Results from ROC curve analysis showed the sensitivity and specificity of PLR to predict early DKD were 83.7% and 82.6%, respectively.

Conclusions: PLR may be a potential hematologic parameter that can be used to predict early DKD.

Keywords

retrospective analysis, diabetic kidney disease, platelet to lymphocyte ratio

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Introduction

Diabetes mellitus (DM) is an endocrine system disease which is prevalent and causes health burden worldwide.[1] Over 10% of the world's population is estimated to have DM or be at high risk of developing DM.[2] Patients with DM whose glucose levels are not well controlled usually presented with many complications such as DKD, diabetic retinopathy, diabetic foot, atherosclerotic cardiovascular diseases and heart failure.[3] As the most common complication in DM patients, DKD is the main cause of death or renal failure in end-stage renal disease (ESRD).[4] If the kidney damage in patients with DM can be detected early, further damage will be prevented. Although the early diagnosis of DKD mainly depends on the detection of microalbuminuria in the clinical setting, microalbuminuria test is easily affected by various factors.[5] Therefore, it is of great significance to explore more sensitive, specific and noninvasive biomarkers for early diagnosis of DKD.

Platelet to lymphocyte ratio (PLR) is a new type of nonspecific inflammatory marker, which has been widely used in the monitoring and prognosis prediction of many respiratory, digestive diseases and tumors.[6] Previous study demonstrated that the PLR of systemic lupus erythematosus (SLE) patients with nephritis is higher than that of SLE patients without nephritis, indicating that PLR may be used to predict the occurence of lupus nephritis.[7] Another report showed that patients with higher PLR had lower survival rate and worse prognosis.[8] A recent study showed that PLR and neutrophil count are

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independent prognostic factors for metastatic renal cell carcinoma (mRCC).[9] In addition, PLR can be used to predict disease activity in SLE patients and the best PLR cut-off value was 132.9.[10]

Therefore, PLR is of great value in the prediction of progression and prognosis of many diseases. Currently there are few reports on PLR used to predict DKD. A recent report has found that Type 2 diabetic patients with proteinuria had significantly higher PLR levels than that of diabetic patients without proteinuria.[11] Therefore, the purpose of this study is to explore whether PLR can be used to predict early DKD in patients with DM.

Materials and Methods

One hundred and eighty-three patients with type 2 diabetes who were hospitalized in Jingzhou Central Hospital, Hubei Province from August 1, 2019 to December 1, 2019 were enrolled for this study. Fouty-nine cases were DM group with early DKD and 134 cases were DM group with normal renal function. The inclusion criteria for the groups were as follows :(1) DM group with early DKD were Urinary Albumin Creatinine Ratio (UACR) ≥30 mg/g but < 300 mg/g; Simultaneously, DM group with normal renal function were UACR < 30 mg/g and glomerular filtration rate (eGFR) ≥30 ml / (min•1.73m^2) according to the American Diabetes Association (ADA) guideline in 2021;(2) The enrolled patients have not taken drugs affecting renal function recently. The exclusion criteria were as follows: (1) there are other endocrine diseases except DM, and patients with cardiovascular and urinary system immune diseases; (2) Patients with primary nephropathy, renal artery stenosis, and renal diseases caused by heart, liver and other systemic diseases.

The blood samples were collected in the EDTA-K2 anticoagulant tubes. The monocyte (M), neutrophil (N), platelet (P) and lymphocyte (L) were measured by Sysmex XN3000.

The Graphpad Prism 5.0 was used for data analysis. Chi-square was used to analyze the difference of age and gender between the groups. The independent sample t-tests were used to compare the differences between early DKD group and the DM group with normal renal function. The receiver operating curve (ROC) and the area under the curve (AUC) were calculated to compare each parameter. The AUCs of these comparative biomarkers were compared by Delong method. A *P*-value <0.05 was considered statistically significant.

Results

Patients Demorgraphics

Patients demorgraphics were lised in Table 1. One hundred and eighty-three patients with type 2 diabetes were enrolled in this retrospective analysis, among which 134 patients were DM with normal renal function while 49 were DM with early DKD. There was no significant difference in age and gender between DM group with normal renal function and early DKD group as shown in Table 1.

Table 1. Comparison of general clinical data between DM with normal renal function (DMNRF) and DM with early diabetic kidney disease (DMEDKD).

Group	DMNRF (n = 144)	DMEDKD(n = 49)	*P*
Age	54.39 ± 11.14	55.79 ± 12.69	0.14
Male	82 56.9%)	31 63.3%)	0.31

Data are presented as mean ± standard deviation(SD).
Abbreviations: DMNRF, DM with normal renal function; DMEDKD, DM with early diabetic kidney disease.

Table 2. Hematologic parameters in DM with normal renal function (DMNRF) and DM with early diabetic kidney disease (DMEDKD).

Group	DMNRF	DMEDKD	*P*
N (X10^9)	3.52 ± 1.69	4.61 ± 3.09	<0.001
L (X10^9)	1.81 ± 0.62	1.91 ± 0.64	0.33
P (X10^9)	198 ± 63.47	209.38 ± 84.38	0.32
M (X10^9)	1.14 ± 0.19	0.48 ± .22	<0.01
NLR	2.20 ± 1.66	3.03 ± 3.76	0.04
NMR	9.56 ± 3.77	9.88 ± 3.91	0.61
PLR	119.73 ± 53.5	54.89 ± 22.39	<0.001

Abbreviations: N, Neutrophil; L, Lymphocyte; P, Platelet; M, Monocyte; NLR, Neutrophil-to-Lymphocyte ratio; NMR, Neutrophil-to-Monocyte ratio; PLR, Platelet-to-Lymphocyte ratio; DMNRF, DM with normal renal function; DMEDKD, DM with early diabetic kidney disease.

Differential Hematologic Parameters in DM Patients with or Without Early DKD

In the early DKD group, N was higher ($P < 0.001$) while M was lower ($P < 0.01$) than those in DM group with normal renal function. The NLR value was higher ($P = 0.04$) but the PLR value was lower ($P < 0.001$) in the early DKD group than that in DM group with normal renal function. And there is no significant difference in L, P, neutrophil / monocyte ratio (NMR) between the two groups as shown in Table 2.

ROC Analysis for the Differential Hematologic Parameters Between DM Patients with or Without Early DKD

We further performed the receiver operation characteristic curve (ROC) analysis for the 4 differential hematologic parameters (N, M, NLR, PLR) in the early DKD group and the area under the curve (AUC) were calculated as shown in Figure 1 and Table 3. As shown in Table 3, the sensitivity and specificity of PLR was 83.7% and 82.6%, respectively. Although the sensitivity of NLR was 90.24%, the specificity (45.9%) was much lower than that of PLR. In addition, the sensitivity of N, M (55.1%, 57.1%) was lower than PLR (83.7%) and the specificity of N,M (74.3%, 72.9%) was also lower than PLR (82.6%). Furthermore, the positive and negative predictive values of PLR were higher than those of NLR, M, N groups. As shown in Table 4, the pairwise comparision (M ～PLR, N ～PLR, NLR～ PLR) of ROC curves were statistically significant *($P < 0.001$)*.

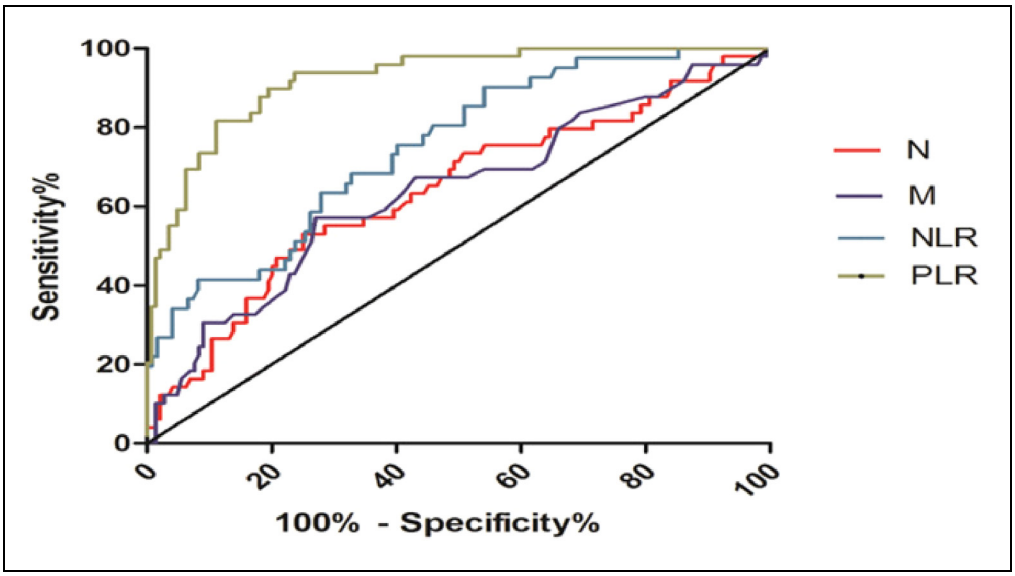

Figure 1. ROC curve of each index in DM with early diabetic kidney disease (DMEDKD). Diagnostic values of N, M, NLR, PLR were shown. Abbreviations: N, Neutrophil; M, Monocyte; NLR, Neutrophil-to-Lymphocyte ratio; PLR, Platelet-to-Lymphocyte ratio.

Table 3. Evaluation of the effect of each index in the diagnosis of DM with early diabetic kidney disease (DMEDKD).

DMEDKD	AUC	*p*	Cut off value	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)
N(x10^9/L)	0.638	<0.001	4.08	55.1	74.3	42.2	82.9
M(x10^9/L)	0.638	<0.01	0.45	57.1	72.9	41.8	83.3
NLR	0.751	0.04	1.56	90.24	45.9	35.9	93.3
PLR	0.922	<0.001	68.86	83.7	82.6	62.1	93.7

Abbreviations: DMEDKD, DM with early diabetic kidney disease; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value. N, Neutrophil; M, Monocyte; NLR, Neutrophil-to-Lymphocyte ratio; PLR, Platelet-to-Lymphocyte ratio.

Table 4. Pairwise comparison of ROC curves by Delong method.

P value	
M∼N	**0.947**
M∼NLR	**0.308**
N ∼NLR	**0.093**
M ∼PLR	**<0.001**
N ∼PLR	**<0.001**
NLR∼ PLR	**<0.001**

Abbreviations: N, Neutrophil; M, Monocyte; NLR, Neutrophil-to-Lymphocyte ratio; PLR, Platelet-to-Lymphocyte ratio.

Discussion

Management of diabetic patients with complications brings huge economic burden to their family and the society. Most of the complications, such as diabetic nephropathy is usually progressing slowly without obivious clinical manifestations, which may eventually progress to renal failure. Therefore, it is essential to identify novel non-invasive biomarkers that can be used to predict early DKD. In this study, the hematologic parameters from 134 DM cases with normal renal function and 49 cases with early DKD were retrospectively analyzed. The area under ROC curve of PLR in early DKD group was significantly higher than that of NLR, N and M. The sensitivity (83.7%) and specificity (82.6%) of PLR were also higher than those of N, M groups, which indicated that PLR is a better biomarker for the prediction of early diabetic nephropathy in diabetic patients. As shown in Table 3, the cut off value of PLR is 68.86 which means when PLR < 68.86, patients are more likely to develop to early DKD. A recent study supported our conclusion that PLR could be used to predict renal function in patients with rapidly progressive glomerulonephritis (RPGN), and they found that PLR was significantly higher in patients with preserved renal function in comparison to patients who required maintenance hemodialysis.[12] Another report demonstrated that PLR is a predictor of clinical outcomes in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors.[13] It should also be noted that machine learning(ML) methods can further improve the accuracy of the prediction (AUC); as this ML method has been widely used in clinical practice.[14]

GFR is the most common prognostic biomarker for predicting ESRD in clinical practice and albuminuria is aslo a traditional diagnosis biomarker which strongly predicts progression of DKD but it lacks specificity and sensitivity for ESRD.[15] In addition to the traditional diagnosis methods for DKD, many potential biomarkers have been investigated. Non-coding RNAs, such as

microRNAs (miRNAs) as new diagnostic markers for DKD have attracted extensive attention. Previous study demonstrated that the level of miR-31 was significantly lower in patients with DKD than that of diabetic patients without complications.[16] Another study indicated that the expression levels of miR-27b-3p and miR-1228-3p in the urine were able to discriminate DKD patients from other glomerulonephritis in diabetic patients.[17] Collectively, results from these studies pointed out that miRNAs may be used as potential biomarkers for predicting DKD in patients with type 2 DM.

With the continuous development of diagnosis and treatment methods, a more standardized and effective individualized (personalized) diagnosis and treatment regimen for diabetic nephropathy patients will be available, which will improve the prognosis of diabetic patients with nephropathy.

However, our current study has a few limitations, one of which is that there were only 183 cases in total, with merely 49 patients with early DKD. Considering the relatively small patient population in this analysis, more clinical cases are needed to confirm our findings in future study and multivaraible regression model can also be used for the prediction purpose. Another limitation is that this is a case control study that the prevalence of the disease in this study cannot reflect its prevalence in the population. In addition, this is the cross-sectional rather than longitudinal design and such design cannot confirm the causal relationship. Lastly, we did not analyze the prognosis of the enrolled cases. In order to address these limitations, another follow-up study is in progress.

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Author Contributions

Xu Chen and Qinhua Wang was involved in the paper drafting, responsible for data collection and data analysis; Chengbin Li was in charge of the research design and critical revision of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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