The prognostic value of lymphocyte-to-monocyte ratio in nephropathy of type 2 diabetes mellitus

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Background Inflammatory markers like interleukin-1, 6, and 8, transforming growth factor-β (TGF-β)1, and tumor necrosis factor-α have been found to be associated with diabetic nephropathy (DN), indicating that its pathogenesis may be inflammatory. These inflammatory markers are not routinely used, so, creating the need for easily and routinely done markers aim to enhance the prognostic process of diabetic microvascular complications. Lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) can be routinely assessed, in addition to being considered as predictors for the survival of patients in renal diseases and malignancies.

Aim The aim was to evaluate the prognostic value of LMR in DN of type 2 diabetes mellitus, and to compare it with other ratios: NLR and PLR.

Patients and methods A case–control study including 100 type 2 diabetes mellitus patients and 25 apparently healthy controls. It was carried out at the inpatient and outpatient clinics, Internal Medicine Department, Al-Azhar University Hospital, New Damietta. Three groups were formed according to urinary albumin-to-creatinine ratio; group I, type 2 diabetics with normoalbuminuria, group II, type 2 diabetics with increased albuminuria, with further division into group IIA: with microalbuminuria/group IIB: macroalbuminuria or overt DN, and group III: controls. Full history, clinical examination, and laboratory tests: urinary albumin-to-creatinine ratio and complete urine analysis, complete blood count with assessment of LMR, NLR, and PLR, beside, blood sugar, HbA1c, renal function with assessment of estimated glomerular filtration rate, liver function, abdominal ultrasonography, fundus examination, and ECG were done for all the participants.

Results The LMR mean was 2.4/2.8/3.2/2.1 in group I/IIA/IIB/III, respectively, showing the increasing ratios in parallel with the progression of DN severity and albuminuria through the groups, with the highest ratios in group IIB of overt DN. The NLR mean was 1.8/2.9/3.7/1.2 and the PLR mean was 175, 8/249, 2/277, 3/108, 3 in the corresponding group. Receiver operating characteristic curve analysis for ratios between groups I and IIA demonstrated that with a best cutoff point of 2.66 for the LMR, the sensitivity was 44%, the specificity: 92% (the ability of the LMR to predict DN risk); 2.2 for the NLR, the sensitivity: 84%, the specificity: 98%; 207 for the PLR, the sensitivity: 72%, and the specificity: 80%. So, in predicting the DN risk, NLR came first as regards the specificity followed by LMR and then PLR, but followed by PLR and then LMR as regards the sensitivity.

Conclusion LMR may be considered as a surrogate inflammatory marker for DN in early stages and in between stages, but it is not better than NLR as a screening tool for DN diagnosis.

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Introduction

Approximately, 25% of type 2 diabetes mellitus (T2DM) patients develop diabetic nephropathy (DN) [1], which is a clinical syndrome consisting of persistent albuminuria (300 mg/g creatinine or >300 mg/24 h), glomerular filtration rate (GFR) progressive decline down to end-stage renal disease, arterial hypertension, and increased cardiovascular morbidity and mortality [2]. However, the albuminuria degree is not necessarily running in parallel with disease progression in T2DM [3]. Alteration of the immune system in diabetes results in the production of elevated levels of circulating proinflammatory cytokines and acute-phase proteins leading to chronic inflammation that induces microvascular and macrovascular complications with organ dysfunction in DM [4,5].

To enhance the diagnostic and prognostic processes for diabetic complications, there is continuous search for routinely done, easy, sensitive, and cost-effective inflammatory markers other than cytokines, especially those correlating well with the early development and with the progression of DN. In this respect, the relationship between microvascular complications of diabetes and the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) has been discussed by some studies which reported that the NLR and PLR are associated with diabetes and its complications [6,7].

Monocytes through the presentation of antigen to lymphocytes connect their innate immune system to

the adaptive immune system of lymphocytes [8]. In addition, monocytes/macrophages exert important roles in vascular and adipose tissues. Monocytes can be polarized as M1 cells which are inflammatory or M2 cells which are anti-inflammatory [9]. The lymphocyte-to-monocyte ratio (LMR) is a novel inflammatory biomarker that reflects the balance between a favorable prognostic outcome (lymphocytes) and an unfavorable one (monocytes) [10]. Not only the relative numbers, but also the function of both cells are essentials for individual's response against infection, and LMR in the peripheral circulation may represent the effective capacity of the individual's immune system [8]. LMR prognostic value has been documented in diabetic retinopathy (DR) [11] and in various tumor studies [10–13].

The advantages of LMR, NLR, and PLR over other cell parameters, for example, total leukocyte counts, neutrophils, and lymphocytes include their stability against physiological, physical, and pathological factors which can induce white blood cells (WBC) count variability, and also they may represent inflammatory and immune signaling in diabetic microvascular complications like DR [11].

Aim

The aim was to assess the relationship between DN of T2DM and LMR as a routinely, easily done, and cost-effective inflammatory marker and to compare its prognostic value with other complete blood count (CBC) ratios.

Patients and methods

Study design

This study was conducted from October 2017 to April 2018. The study included 100 T2DM patients and 25 apparently healthy controls. The study was according to the Ethics Board of Al-Azhar University. It was carried out at the inpatient and outpatient clinics of the Internal Medicine Department, Al-Azhar University Hospital, New Damietta.

Ethical aspects

Informed consent was taken from each participant.

Exclusion criteria

The exclusions involved T1DM; infection or recent history of infection in the past 1 month, for example, otitis media, viral infection or pyrexia of unknown origin, systemic disorder such as chronic liver, cardiovascular, or chronic kidney diseases, malignancy, blood disorders, autoimmune disorders, nephrotic syndrome, urolithiasis, renal artery stenosis, dehydration state, patients having low GFR without microalbuminuria and patients taking anti-inflammatory drugs, steroids, renin angiotensin aldosterone system antagonists, or alcohol.

Study protocol

All individuals were subjected to full history, clinical examination with stress on the duration of DM, presence or absence of microvascular or macrovascular complications, and laboratory tests: urinary albumin-to-creatinine ratio (UACR) and complete urine analysis, CBC (using Sysmex XS-500i, Automated Hematology Analyzer XS series; Sysmex Corporation, Chuo-ku, Kobe, Japan) with assessment of LMR, NLR, and PLR, fasting blood sugar, 2 h postprandial blood sugar, HbA1c, renal function with assessment of eGFR, liver function, abdominal ultrasonography, fundus examination, and ECG.

Sample collection

A volume of 5 ml of venous blood was taken from the participant. For CBC measurement, 2 ml was added to an EDTA tube, while the other 3 ml was collected in a plain tube and left to clot and then centrifuged and finally the serum was separated. Measurement of liver and kidney functions has been done using an automated biochemistry analyzer (Beckman Coulter AU480, Beckman Coulter Ireland Inc., Lismeehan, O' Callaghan' s Mills, Co. Clare, Ireland).

Laboratory assessment

Daily urinary albumin excretion was assessed by a UACR using fasting mid-stream urine samples, according to which the individual was involved in one of these groups. Group I: type 2 diabetics with normoalbuminuria (UACR of less than 30 mg/g), group II: type 2 diabetics with increased albuminuria, with further division into group IIA, with microalbuminuria (UACR 30-300 mg/g), group IIB: with macroalbuminuria or overt DN (UACR of greater than 300 mg/g), and group III: apparently healthy controls matched for age and sex [14]. The Chronic kidney disease-Epidemiology collaboration (CKD?EPI) equation was used to calculate eGFR. LMR was assessed by dividing the absolute lymphocytic count on the absolute monocytic count, NLR by dividing the absolute neutrophilic count on the absolute lymphocytic count, and PLR by dividing the platelet count on the absolute lymphocytic count.

Statistical methodology

Using the International Business Machines Corporation (IBM) Statistical Package for Social Sciences (IBM

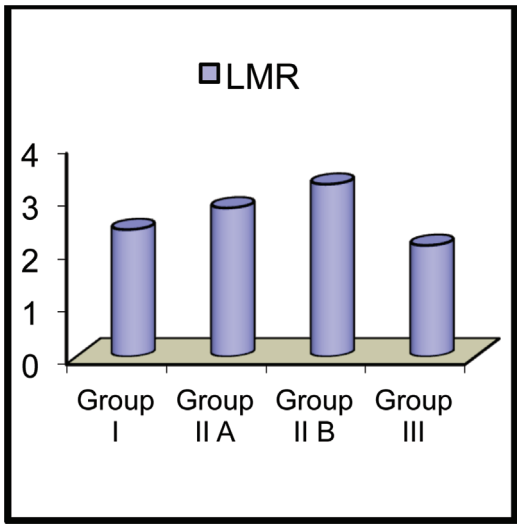
Table 1 Comparison between the studied groups as regards demographic data and laboratory investigations

	Group I (mean ±SD)	Group IIA (mean ±SD)	Group IIB (mean ±SD)	Group III (mean ±SD)	Tests	*P* value
Age (years)	47.10±8.35	47.60±7.39	57.28±6.57	45.76±7.14	χ^2=12.731	<0.001
Weight (kg)	79.76±5.59	79.76±5.64	83.56±7.21	78.84±5.57	χ^2=3.208	0.026
FBS (mg/dl)	169.86±42.66	180.92±32.91	186.36±30.82	88.36±12.39	*F*=45.955	<0.001
PPBS (mg/dl)	266.68±45.84	269.36±40.55	310.44±43.10	130.12±9.42	*F*=100.987	<0.001
HbA1c%	7.64±0.96	8.73±1.03	8.82±1.08	5.31±0.22	*F*=80.857	<0.001
WBCs (10^3/ml)	5.26±1.54	5.02±1.31	5.76±1.07	5.97±0.80	*F*=3.194	0.026
Neutrophils (10^3/ml)	3.20±0.89	3.14±0.83	4.02±0.88	3.19±0.58	*F*=6.899	<0.001
Lymphocytes (10^3/ml)	1.75±0.53	1.11±0.36	1.14±0.34	2.54±0.48	*F*=54.507	<0.001
LMR	2.41±0.55	2.82±0.64	3.27±0.68	2.11±0.30	*F*=21.448	<0.001
NLR	1.82±0.31	2.94±0.79	3.65±0.86	1.24±0.19	*F*=101.169	<0.001
PLR	175.76±63.42	249.24±93.47	277.32±92.99	108.32±36.32	*F*=28.016	<0.001
eGFR	97.74±17.11	95.75±21.38	60.21±18.03	104.80±13.47	*F*=33.671	<0.001
Serum uric acid (mg/dl)	4.10±0.83	4.32±1.03	5.40±1.28	3.45±0.80	*F*=17.853	<0.001
Serum creatinine (mg/dl)	0.94±0.17	0.98±0.24	1.43±0.42	0.89±0.09	*F*=27.606	<0.001
Urine albumin (mg/dl)	15.28±5.33	196.6±61.61	1038.13±261.8	5.28±2.15	*F*=265.809	<0.001
UACR	19.1±5.53	151.20±77.04	451.36±86.01	6.60±2.19	*F*=451.053	<0.001

F, one-way analysis of variance; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PPBS, 2 h postprandial blood sugar; UACR, urinary albumin-to-creatinine ratio; WBC, white blood cells.

SPSS) version 20 data were collected then coded, revised, and lastly entered. Qualitative data were presented in the form of numbers and percentages while quantitative data with parametric distribution in the form of means, SD and ranges and quantitative data with nonparametric distribution in the form of median with interquartile range. Comparison of qualitative data between two groups was done using χ^2-test, but when the expected count is found in any cell to be less than 5, Fisher's exact test was used instead. One-way analysis of variance test was used to compare between more than two groups when quantitative data are of parametric distribution. Kruskal–Wallis test was used to compare between more than two groups when the quantitative data are of no parametric distribution. Whole tests were two sided. When the *P* value is less than 0.05, it was considered statistically significant, less than 0.001: highly statistically significant, and greater than or equal to 0.05: nonstatistically significant.

Figure 1

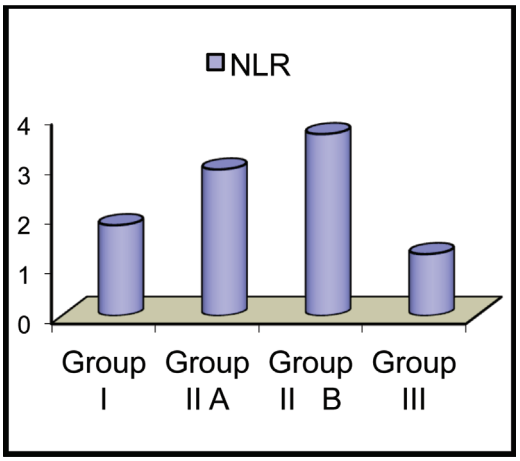


Lymphocyte-to-monocyte ratio in the studied groups.

Results

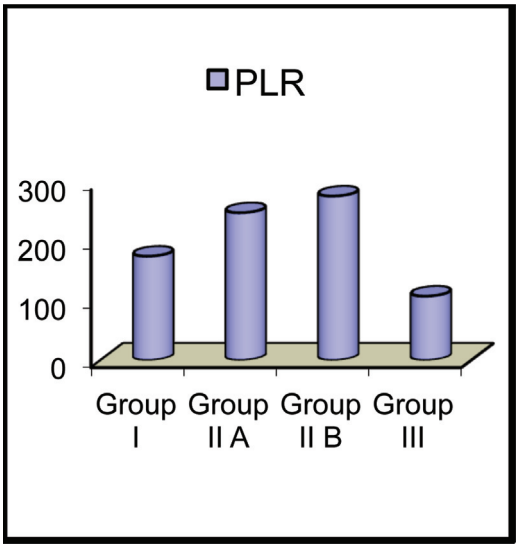
In our study, there was a highly statistically significant: increase as regards LMR, NLR, PLR, neutrophils, urine albumin, UACR, uric acid, serum creatinine, fasting blood sugar, 2 h postprandial blood sugar, age, and HbA1c; decrease as regards to lymphocytes and eGFR; statistically significant increase as regards WBCs and weight in group IIB versus groups I, IIA, and III (with exception of increased mean of WBCs in group III vs. group IIB, and decreased mean of lymphocytes in group IIA vs. IIB). Age was cross-matched except for group IIB that showed an increased mean of age as the long duration of the disease is associated with advanced development of complications. It was noted that most of the parameters increased or decreased in parallel with disease severity progression. There was no statistically significant difference as regards sex and PLT in the studied groups. LMR mean was 2.4/2.8/3.2/2.1 in group I/IIA/IIB/III, respectively, showing the increasing ratios in parallel with the progression of DN severity and albuminuria through the groups, with the highest ratio in group IIB of overt DN. NLR mean was 1.8/2.9/3.7/1.2, and the PLR mean was 175, 8/249, 2/277, 3/108, 3 in the corresponding group (Table 1 and Figs 1–5). There was a statistically

Figure 2



Neutrophil-to-lymphocyte ratio in the studied groups.

Figure 3

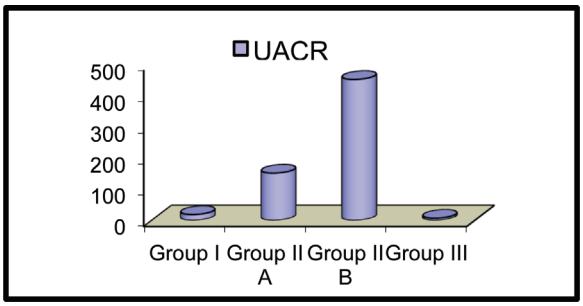


Platelet-to-lymphocyte ratio in the studied groups.

significant increase in urinary protein, cast, and red blood cells especially in group IIB, but there was no statistically significant difference in urinary WBCs as regards the studied groups (Table 2).

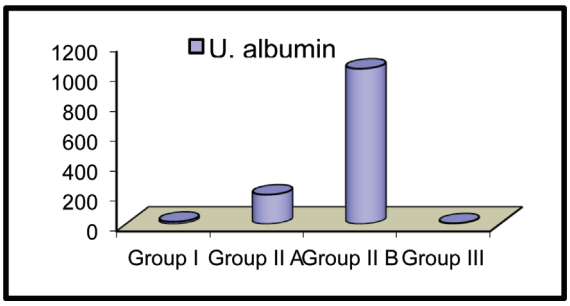
In group I: LMR showed a positive correlation with urine albumin and alanine aminotransferase; NLR showed a positive correlation with urine albumin, UACR, and eGFR and negative correlation with lymphocytes, while the PLR showed a positive correlation with PLT, urine albumin, and UACR and negative correlation with WBCs, neutrophils, lymphocytes, and alanine aminotransferase (Table 3). In group IIA: LMR showed a positive correlation with urine albumin and aspartate aminotransferase; NLR showed a positive correlation with PLR, HbA1c, urine albumin, and UACR, and negative correlation

Figure 4



Urinary albumin-to-creatinine ratio in the studied groups.

Figure 5



Urine albumin in the studied groups.

with lymphocytes, while the PLR showed a positive correlation with HbA1c, PLT, urine albumin, and UACR and negative correlation with WBCs, neutrophils, and lymphocytes (Table 4). In group IIB: LMR showed a negative correlation with PLT, urine Albumin, and serum creatinine, NLR showed a positive correlation with PLR, urine Albumin, and UACR, and negative correlation with lymphocytes, while the PLR showed a positive correlation with PLT, urine albumin, and UACR and negative correlation with WBCs, neutrophils, and lymphocytes (Table 5).

Between groups I and IIA, receiver operating characteristic curve analysis demonstrated that with a best cutoff point of 2.66 for the LMR, the sensitivity was 44%, the specificity: 92%, area under the curve (AUC): 0.702, negative predictive value (NPV): 76.7%, and positive predictive value (PPV): 73.3%; 2.2 for the NLR, the sensitivity: 84%, the specificity: 98%, AUC: 0.962, NPV: 90.7%, and PPV: 95.2%; 207 for the PLR, the sensitivity: 72%, the specificity: 80%, AUC: 0.758, NPV: 85.1%, and PPV: 64.3% (Table 6 and Figure 6). While between groups IIA and IIB, the results were 2.8 for the LMR, the sensitivity was 52%, the specificity: 84%, AUC: 0.691, NPV: 63.6%, and PPV: 76.5%; 2.92 for the NLR, the sensitivity: 64%, the specificity: 88%, AUC: 0.753, NPV: 71%, and PPV: 84.2%; 288 for the PLR, the sensitivity: 76%, the specificity: 84%, AUC:

Table 2 Comparison between the studied groups as regards urine analysis

	Group I [*n* (%)]	Group IIA [*n* (%)]	Group IIB [*n* (%)]	Group III [*n* (%)]	$\chi 2$	*P* value
Protein						
+	0 (0.0)	1 (4.0)	20 (80.0)	0 (0.0)	101.064	<0.001
++	0 (0.0)	0 (0.0)	2 (8.0)	0 (0.0)		
Nil	50 (100.0)	24 (96.0)	3 (12.0)	25 (100.0)		
Cast						
Granular	0 (0.0)	2 (8.0)	11 (44.0)	0 (0.0)	43.169	<0.001
Hyaline	3 (6.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Nil	47 (94.0)	23 (92.0)	14 (56.0)	25 (100.0)		
Urinary WBCs (mean±SD)	3.68±2.69	4.68±3.40	4.68±3.40	3.28±2.79	1.515	0.214
Urinary RBCs (mean±SD)	2.12±2.07	2.20±2.10	3.04±2.35	1.80±0.92	4.379	0.006
Post-hoc test and χ^2-test						
	Group IIA vs. group I		Group IIA vs. group IIB		Group I vs. group III	
Protein	0.155		<0.001		NA	
Cast	0.064		0.004		NA	
WBCs	0.178		1.000		0.589	
RBCs	0.876		0.157		0.020	

RBC, red blood cells; WBC, white blood cells.

Table 3 Correlation between lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio as regards all parameters in group I

	LMR		NLR		PLR	
	r	*P* value	*r*	*P* value	*r*	*P* value
LMR			0.052	0.718		
PLR	–0.247	0.083	0.240	0.094		
WBCs	0.174	0.226	0.088	0.544	–0.555	0.001
PLT	–0.143	0.321	–0.002	0.989	0.542	0.001
Neutrophils	0.243	0.089	0.270	0.058	–0.593	0.001
Lymphocytes	0.219	0.126	–0.300	0.034	–0.766	0.001
Urine albumin	0.453	0.028	0.542	0.003	0.351	0.022
UACR	0.016	0.913	0.300	0.034	0.345	0.022
eGFR	0.132	0.362	0.542	0.003	0.044	0.763
ALT	0.333	0.018	0.050	0.729	–0.351	0.012

ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelet; UACR, urinary albumin-to-creatinine ratio; WBC, white blood cells.

Table 4 Correlation between lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio as regard all parameters in group IIA

	LMR		NLR		PLR	
	r	*P* value	*r*	*P* value	*r*	*P* value
LMR			0.287	0.164		
PLR	–0.019	0.930	0.440	0.028		
HbA1c	0.164	0.432	0.662	0.001	0.432	0.031
WBCs	0.112	0.595	0.002	0.991	–0.469	0.018
PLT	0.174	0.406	–0.008	0.969	0.610	0.001
Neutrophils	0.338	0.099	0.111	0.596	–0.553	0.004
Lymphocytes	0.174	0.406	–0.532	0.006	–0.778	0.001
Urine albumin	0.610	0.001	0.559	0.002	0.468	0.038
UACR	–0.141	0.502	0.553	0.004	0.447	0.025
AST	0.447	0.025	0.038	0.856	0.232	0.264

AST, aspartate aminotransferase; eGFR, estimated glomerular-to-filtration rate; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelet; UACR, urinary albumin-to-creatinine ratio; WBC, white blood cells.

0.590, NPV: 66.7%, and PPV: 59.4% (Table 7), and between groups I and III: 2.3 for the LMR, the sensitivity was 50%, the specificity: 84%, AUC: 0.694, NPV: 45.7%, and PPV: 86.2%; 1.5 for the NLR, the sensitivity: 84%, the specificity: 92%, AUC: 0.925, NPV: 74.2%, and PPV: 95.5%; 147 for the PLR, the sensitivity: 68%, the specificity: 88%, AUC: 0.838, NPV: 57.9%, and PPV: 91.9% (Table 8).

Table 5 Correlation between lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio as regard all parameters in group IIB

	LMR		NLR		PLR	
	r	*P* value	*r*	*P* value	*r*	*P* value
LMR			0.160	0.444		
PLR	−0.016	0.940	0.725	0.001		
WBCs	−0.303	0.140	−0.218	0.295	−0.409	0.043
PLT	−0.407	0.043	0.183	0.382	0.579	0.002
Neutrophils	−0.178	0.395	−0.086	0.683	−0.425	0.034
Lymphocytes	−0.165	0.430	−0.744	0.001	−0.813	0.001
Urine albumin	−0.678	0.001	0.579	0.002	0.733	0.001
UACR	−0.120	0.569	0.409	0.043	0.579	0.002
Serum creatinine	−0.429	0.032	−0.074	0.725	0.200	0.338

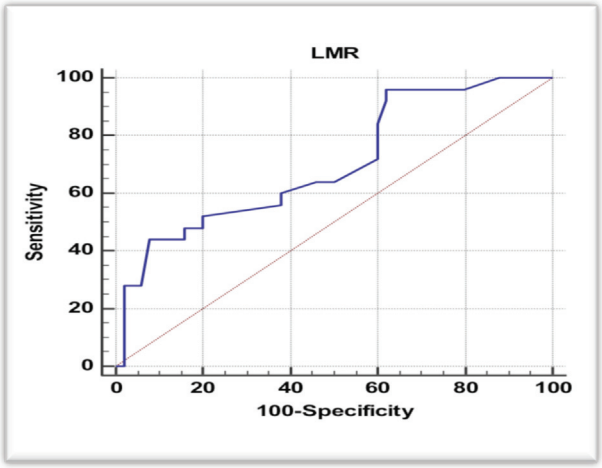
LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelet; UACR, urinary albumin-to-creatinine ratio; WBC, white blood cells.

Table 6 Cutoff point, sensitivity, and specificity of lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio between group I and group IIA

Variables	Cutoff point	AUC	Sensitivity	Specificity	NPV	PPV
LMR	>2.66	0.702	44.00	92.00	76.7	73.3
NLR	>2.2	0.962	84.00	98.00	90.7	95.2
PLR	>207	0.758	72.00	80.00	85.1	64.3

AUC, area under the curve; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PLR, platelet-to-lymphocyte ratio; PPV, positive predictive value.

Figure 6



Cutoff point sensitivity and specificity of lymphocyte-to-monocyte ratio between group Is and IIA.

Discussion

In this study, LMR was significantly higher in type 2 diabetics with macroalbuminuria (overt DN) when compared with type 2 diabetics with normoalbuminuria or microalbuminuria and controls. Also, the ratios were higher in diabetics with microalbuminuria when compared with normoalbuminuric diabetics and controls. In addition, there was significant correlation between LMR and albuminuria. Moreover, the mean LMR levels increased in parallel with DN severity.

Table 7 Cutoff point, sensitivity, and specificity of lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio between group IIA and group IIB

Variables	Cutoff point	AUC	Sensitivity	Specificity	NPV	PPV
LMR	≤2.8	0.691	52.00	84.00	63.6	76.5
NLR	≤2.92	0.753	64.00	88.00	71.0	84.2
PLR	≤288	0.590	76.00	48.00	66.7	59.4

AUC, area under the curve; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PLR, platelet-to-lymphocyte ratio; PPV, positive predictive value.

Table 8 Cutoff point, sensitivity, and specificity of lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio between group I and III

Variables	Cutoff point	AUC	Sensitivity	Specificity	NPV	PPV
LMR	>2.3	0.694	50.00	84.00	45.7	86.2
NLR	>1.5	0.925	84.00	92.00	74.2	95.5
PLR	>147	0.838	68.00	88.00	57.9	91.9

AUC, area under the curve; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PLR, platelet-to-lymphocyte ratio; PPV, positive predictive value.

In our study, the best cutoff value of LMR was 2,66 with sensitivity and specificity for DN diagnosis being 44 and 92%, respectively, with AUC at 0.702, PPV 73% and NPV 76,7%. To our knowledge, no study had discussed the relation between DN and LMR. As regards DR, Yue *et.al.* [11], in their study found the cutoff value of LMR to be 2.25, with sensitivity and specificity for diagnosis of DR being 47.1 and 69.6%, respectively, with AUC at 0.581, PPV 59.82% and NPV 57.80%. The difference in the cutoff between DN and DR risk diagnosis should be evaluated by further studies.

In the present study, the best cutoff value of NLR for DN diagnosis was 2.2, the sensitivity: 84%, the specificity: 98%; and for PLR was 207, the sensitivity: 72%, the specificity: 80%. In agreement with our results, Huang *et.al.* [15] found NLR to be higher in diabetics with nephropathy (2.4±0.6) than those without nephropathy (2.2±0.6). Abdelaziz *et al.* [16] found NLR and PLR to be significantly associated with DN and considered both as predictors and prognostic markers for DN.

In addition, Akbas *et al.* [6] documented the increase of NLR with the increase of albuminuria and also, according to them, PLR can predict the inflammation and albuminuria in diabetics. Moreover, Hudzik *et al.* [17] considered PLR as an independent risk factor for mortality, early or late, in diabetics. Descamps-Latscha *et al.* [18] found a positive correlation between PLR and NLR, interleukin-6, and tumor necrosis factor-α in diabetics with end-stage renal disease.

Our study showed a significant decrease in eGFR in macroalbuminuria versus microalbuminuria and the later versus normoalbuminuric diabetics and all versus controls. In agreement, Sagar *et.al.* [19] has shown that albuminuric patients had significantly low eGFR than the normal albuminuric patients.

In about one-third of the diabetic patients, renal function decline occurs before the presence of microalbuminuria, which decreases the reliability of microalbuminuria to monitor, alone, the development and progression of DN [20]. This elevates the need for other biomarkers that correlate well with DN incidence and progression.

Chronic inflammation appears to underlie most of the chronic diseases, including cardiovascular disease, T2DM, chronic kidney disease, Alzheimer's disease, and cancer [21]. As NLR can be a marker of systemic inflammation and predictor of mortality in cardiovascular diseases and survival in tumors [22,23], LMR can, also, be.

The inflammatory process within the diabetic kidney is mediated by proinflammatory cytokines, reactive oxygen species, growth factors, and metalloproteinase; these are produced from leukocytes (neutrophils, lymphocytes, and macrophages) infiltrating the renal tissues. The homing of leukocytes into renal tissues is probably mediated by intercellular adhesion molecule-1 and the chemokines CX3CL1 and CCL2 [24]. These leukocytes are activated by advanced glycation end products or reactive oxygen species or cytokines [25–27]. In addition, the immune cells participate in the vascular injury in DN, and the infiltrating macrophages may be behind mesangial cell proliferation [24].

Total and differential WBC counts are associated with the albuminuria degree in T2DM patients [28]. Neutrophilia and relative lymphocytopenia were shown to be independent inflammatory markers in diabetic microangiopathies in Caucasians [29–34].

Lymphocytes are key mediators of immunosurveillance and lymphopenia is considered a surrogate marker of the immunological incompetence of the host [35]. Monocytes are considered an indicator of systemic inflammation. Tissue macrophages exist in two major states: M1which is classically activated and inflammatory and M2 that is alternatively activated and anti-inflammatory [36]. Study of Fadini *et al.* [9] showed a marked reduction of M2 in T2DM while M1 were unchanged, resulting in increased M1/M2 polarization ratio in DM. They concluded that the proinflammatory status of DM may be due to the defect in M2 (anti-inflammatory) rather than an excess in M1 (proinflammatory).

LMR in peripheral circulation, a novel inflammatory marker, represents the balance between the favorable prognostic outcome (lymphocyte) and the unfavorable one (monocyte) reflecting the immunological competence [10]. LMR prognostic value was demonstrated in tumor studies [10,12,13] and DR [11]. Moreover, LMR was shown to be a valuable screening tool for influenza [37], marker for metastatic risk and survival prognosis in nasopharyngeal carcinoma [38], and in extranodal natural killer/T-cell lymphoma [35].

The limitations of this study are the small numbers of the patients, being all Egyptians; so, the influence of ethnic diversity is not discussed, and also the need to study the dynamic changes in DN progression and relationship with different treatments.

Conclusion

In our study, LMR as an inflammatory marker can predict the risk of nephropathy in type 2 diabetic patients and this refers to the inclusion of inflammation and vascular dysfunction in DN pathogenesis. The calculation of LMR values in T2DM patients can be a cheap, routinely used, and specific marker for early DN diagnosis. While NLR

was better than both LMR and PLR as a DN risk predictor, LMR specificity was higher than that of PLR, which had a higher sensitivity than that of LMR.

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Conflicts of interest
There are no conflicts of interest.

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