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Original Article

Mean platelet volume and neutrophil to lymphocyte ratio in prediction of early diabetic nephropathy in type 2 diabetics

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1. Introduction

Diabetes mellitus (DM) is rapidly becoming one of the most frequent non-communicable diseases globally [1]. The inflammatory process plays a significant part in the pathogenesis of type 2 diabetes and precedes the onset of the disease [2,3]. Subclinical inflammation contributes to further deepening of metabolic disturbances and finally development of vascular diabetic late complications. Diabetic nephropathy (DN) becomes the most common cause of end-stage renal disease (ESRD) in worldwide. In 2009–2011, diabetes was the primary cause of ESRD in about 42% of diabetic patients in Egypt [4].

Urine albuminuria previously known as microalbuminuria excretion rate can be used to detect and monitor the progression of diabetic nephropathy [5]. About 20%–40% of type 2 diabetics with albuminuria progress to overt nephropathy; and about 20% will develop ESRD after the development of overt nephropathy [6]. There are many limitations of using albuminuria, as the primary marker for kidney function in DM. Urinary albumin excretion is not specific to DN development or progression. Also, urinary albumin is influenced by exercise, high intake of protein and fat, urinary tract infections, and hypertension. It has been determined that 20%–30% of diabetic patients with early DN do not present with urinary albumin excretion [7].

MPV is a surrogate marker of platelet activation; it refers the mean size of platelets. Platelets interact as inflammatory cells. In response to inflammatory stimuli, platelets become activated and tend to be larger [8]. An increase of MPV and its correlation with blood glucose and HbA1c were also noted in prediabetic subjects [9].

Neutrophils to lymphocytes NLR is calculated using results from a complete blood count with differential [10]. NLR has been identified as an inflammatory marker in various disorders [11]. Neutrophilia promotes widespread chonic inflammation, which supports an environment suitable for the pathogenesis of DM and DM-related cardiovascular and renal disease [12]. Hence the aim of this study was to evaluate blood MPV and NLR as a predictive marker for early diabetic nephropathy.

2. Subjects and methods

This prospective study was carried out on (60) patients with T2DM in addition to (20) apparently healthy individuals of matched age and sex as a control group. Patients were selected from the wards and outpatient clinic of Internal Medicine Department, Tanta University Hospital. The study was performed from March 2017 to September 2017. The study was approved by the Ethical Committee of Tanta Faculty of Medicine.

2.1. The participants were classified into

1. **Group 1:** 20 apparently healthy individuals as control.
2. **Group 2:** 30 T2DM patients without DN.
3. **Group 3:** 30 T2DM patients with DN.

2.2. Inclusion criteria

Patients with T2DM - meeting 2017 American Diabetes

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Association diabetes standards and classification [13]- were included in the study. Patients with 24 urinary albumin excretions between (30–300 mg/day) were diagnosed to have micro-albuminuria.

2.3. Exclusion criteria

Patients with any infection e.g.: urinary tract infection, upper respiratory tract infection, any viral infection, blood diseases affecting platelets, neutrophils and lymphocyte, diseases affecting urinary protein excretion (e.g. Nephrotic syndrome, urolithiasis, liver diseases, hypovolemia and dehydration), malignancies, patients on steroid therapy for any reason or patients with type 1 DM were excluded from the study.

All participants were subjected to: Thorough history taking, thorough clinical examination with especial stress on: blood pressure and clinical findings of nephropathy, laboratory tests: blood samples were taken from participants to evaluate: complete blood counts with estimation of hematological parameters as MPV, neutrophil count, lymphocyte count and calculation of NLR, 24 h urine albumin (for patients only), lipid profile (serum cholesterol (TC), triglycerides (TGs), low density lipoprotein (LDL) and high density lipoprotein (HDL), fasting blood glucose (FBG) and 2 h, post prandial blood glucose (PPBG), glycated Hb (HbA1c), erythrocyte sedimentation ratio (ESR), C-reactive protein, calculation of glomerular filtration rate (GFR) according to the diet modification in renal disease [14].All participants provided a written informed consent.

3. Methods

Samples collection: 5 ml of peripheral venous blood were collected under complete aseptic conditions and were divided as follows:

- One ml of peripheral blood was collected on EDTA vacutainers for HbA1c determination and complete blood count (CBC) on ERMA PCE-210 N cell counter together with examination of Lieshman-stained peripheral blood (PB) smears for a differential leucocytic count and calculation of MPV and NLR.
- 4 ml of peripheral blood was collected in plain tube and were allowed to clot for 20 min at room temperature before centrifugation for 5-min at 3500 rpm. Serum sample was separated for routine laboratory investigation, done by Kenolab PRIME 60 (Thermo Scientific, USA). ESR done by Wintergreen method.

24 h **urine** for calculation of albuminuria: albuminuria is measured by Biosystem BTS-350 (Biosystems, Spain), with reference values < 30 mg/24 h.

3.1. Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 21.0, IBM, Armonk, NY, United States of America Quantitative. Data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The following tests were done: independent-samples *t*-test of significance, one-way analysis of variance (ANOVA), Post Hoc test, Chi-square (X^2) test, Pearson's correlation coefficient (r) test, Receiver operating characteristic (ROC curve) analysis with detection of sensitivity and specificity at this cut-off value, positive predictive value (PPV), negative predictive value (NPV). P-value <0.05 was considered significant.

4. Results

The following parameters were significantly higher in DN and diabetic groups in comparison to control group: HbA1c, mean FBG, mean PPS, mean total cholesterol, mean serum triglycerides, ($p = 0.001$) for all. As for mean LDL it was significantly higher in DN group in comparison to control group ($p = 0.028$). While the mean HDL was significantly higher in control group in comparison to DN and diabetic groups ($p = 0.001$) (Table 1). As for the inflammatory markers, the mean CRP was significantly higher in DN and diabetic groups compared to control groups ($p = 0.001$) for both. Also the mean ESR1 was significantly higher in DN group in comparison to diabetic and healthy groups ($p = 0.037$ and 0.007) respectively. The mean ESR2 as well was significantly higher in DN group in comparison to Diabetic and control groups ($p = 0.005$ and 0.001) respectively (Table 1).

As for the renal function: the mean serum urea was significantly higher in DN in comparison to control group ($p = 0.003$), while the mean serum creatinine was significantly higher in DN and diabetic groups in comparison to control group ($p = 0.001$) for both. On the other hand the mean eGFR was significantly higher in control group in comparison to DN and diabetic groups ($p = 0.001$) for both. As regard UAE, there was a significant increase in its level in DN group compared to diabetic group ($p = 0.001$). (Table 2).

Regarding the CBC: The mean Hb level was significantly higher in control group in comparison to diabetic and DN groups ($p = 0.001$). The mean PLT count showed no significant difference between the studied groups ($p = 0.718$). Also the mean MPV showed no significant difference between the three groups

Table 1
Comparison between groups according to demographic and laboratory parameters.

Parameter	Groups	Mean ± SD	P		
Age (Years)	Control	58.15 ± 11.95	0.726		
	Diabetic	60.40 ± 9.98			
	DN	59.10 ± 8.36			
HbA1c (%)	Control	5.54 ± 0.20	0.001*	P1	0.001*
	Diabetic	6.85 ± 0.95		P2	0.001*
	DN	7.35 ± 1.0		P3	0.025*
FBG (mg/dl)	Control	81.60 ± 6.65	0.001*	P1	0.001*
	Diabetic	201.37 ± 55.88		P2	0.001*
	DN	218.70 ± 55.93		P3	0.171
2 PPG (mg/dl)	Control	102.80 ± 5.51	0.001*	P1	0.001*
	Diabetic	264.63 ± 60.99		P2	0.001*
	DN	313.67 ± 55.43		P3	0.001*
Total cholesterol (mg/dl)	Control	147.55 ± 32.15	0.001*	P1	0.001*
	Diabetic	201.87 ± 38.90		P2	0.001*
	DN	203.83 ± 49.07		P3	0.855
Triglyceride (mg/dl)	Control	102.00 ± 24.63	0.001*	P1	0.001*
	Diabetic	185.17 ± 54.64		P2	0.001*
	DN	171.67 ± 40.73		P3	0.234
HDL (mg/dl)	Control	56.95 ± 7.73	0.001*	P1	0.001*
	Diabetic	48.33 ± 7.04		P2	0.001*
	DN	47.83 ± 6.98		P3	0.788
LDL (mg/dl)	Control	102.55 ± 18.05	0.048*	P1	0.235
	Diabetic	112.30 ± 31.13		P2	0.028*
	DN	120.77 ± 30.57		P3	0.249
CRP (mg/l)	Control	4.70 ± 1.92	0.001*	P1	0.001*
	Diabetic	9.27 ± 5.11		P2	0.001*
	DN	9.53 ± 5.30		P3	0.824
ESR1	Control	11.20 ± 4.43	0.017*	P1	0.390
	Diabetic	13.20 ± 7.16		P2	0.007*
	DN	17.60 ± 10.32		P3	0.037*
ESR2	Control	17.55 ± 3.78	0.008*	P1	0.002*
	Diabetic	26.87 ± 9.83		P2	0.001*
	DN	34.40 ± 12.99		P3	0.005*

P1: comparing between healthy group and group 2.
P2 comparing between healthy group and group 3.
P3: comparing between group 2 and group 3.
*; Statistically significant at P-value <0.05.

Table 2
Comparison between the studied groups according to kidney function.

Parameter	Groups	Mean ± SD	P		
Urea (mg/dl)	Control	23.70 ± 6.54	0.013*	P1	0.051
	Diabetic	29.23 ± 8.94		P2	0.003*
	DN	32.13 ± 11.82		P3	0.248
Creatinine (mg/dl)	Control	0.90 ± 0.18	0.001*	P1	0.001*
	Diabetic	1.22 ± 0.24		P2	0.001*
	DN	1.34 ± 0.27		P3	0.073
UAE (mg/d)	Control	NA	0.001*		
	Diabetic	14.43 ± 6.37			
	DN	175.77 ± 62.83			
eGFR (ml/min)	Control	114.65 ± 4.83	0.001*	P1	0.001*
	Diabetic	99.13 ± 12.72		P2	0.001*
	DN	93.37 ± 9.33		P3	0.028*

NA: Not applicable.
* Significant ($p < 0.05$).

Table 3
Comparison between studied groups according to some CBC parameters.

Parameter	Groups	Mean ± SD	P		
Hb (g/dl)	Control	14.18 ± 1.08	0.001*	P1	0.001*
	Diabetic	11.85 ± 1.22		P2	0.001*
	DN	11.91 ± 1.13		P3	0.841
PLT ($X10^3$/mm)	Control	250.50 ± 77.01	0.718	P1	0.584
	Diabetic	262.33 ± 70.56		P2	0.419
	DN	268.00 ± 77.00		P3	0.770
MPV (fl)	Control	8.21 ± 0.47	0.230	P1	0.088
	Diabetic	8.45 ± 0.45		P2	0.309
	DN	8.35 ± 0.54		P3	0.432
Neutrophil ($X10^9$/l)	Control	3.68 ± 0.55	0.001*	P1	0.001*
	Diabetic	4.44 ± 0.47		P2	0.001*
	DN	5.94 ± 0.44		P3	0.001*
Lymphocyte ($X10^9$/l)	Control	2.62 ± 0.46	0.001*	P1	0.004*
	Diabetic	2.96 ± 0.45		P2	0.001*
	DN	3.38 ± 0.26		P3	0.001*
NLR	Control	1.42 ± 0.11	0.001*	P1	0.027*
	Diabetic	1.53 ± 0.23		P2	0.001*
	DN	1.76 ± 0.16		P3	0.001*

* Significant ($p < 0.05$).

($p = 0.230$). The mean neutrophil count, the mean lymphocyte count and the mean **NLR**, all were significantly higher in DN group in comparison to diabetic and control groups ($p = 0.001$) for all. Also all were significantly higher in diabetic group in comparison to control group ($p = 0.001$) for all (Table 3).

According to Table 4, in the diabetic group, there were significant negative correlations between NLR and total cholesterol, eGFR, Hb, and lymphocyte. While there were significant positive correlations between NLR and serum urea, blood creatinine, CRP, and UAE. The same results were documented in Table 4 for correlation of NLR with different parameters in DN group with the addition of a significant positive correlation between NLR and neutrophils (Table 4).

On the other hand MPV showed no significant correlation with any of the previous parameters in both DN and diabetic group (Table 4).

The ROC of NLR showed 96% sensitivity, 91% specificity, 93% positive predictive value, 95% negative predictive value and 94% accuracy (Table 5) and fig. (1). The ROC of MPV showed 76% sensitivity, 66% specificity, 72% positive predictive value, 70% negative predictive value and 72% accuracy (Table 5) and fig. (2).

5. Discussion

T2DM is a serious public health problem, considering its epidemic prevalence levels and high morbidity and mortality rates [15]. It was reported that about 25–40% of patients with T2DM suffered from DN, which considered as the major cause of end stage renal failure [16]. White blood corpuscles and their subtypes are considered as inflammatory markers in different disorders as DM [17].NLR may be considered a novel marker of chronic inflammation as it represents two markers; neutrophils, which represent the active nonspecific mediator initiating the first line of defense and lymphocytes, representing the regulatory or protective component of inflammation [18].

Few studies have evaluated MPV values in hemodialysis (HD) patients as well as in patients with DN or in patients with chronic kidney disease (CKD) stages [19]. The mean platelet count was higher in the diabetic groups than in the control group, but the difference was not statistically significant ($P = 0.718$). This was

Table 4
Correlation between NLR, MPV and different parameters in diabetic and DN groups.

Parameter	NLR				MPV			
	Diabetic group		DN		Diabetic group		DN	
	r	p	r	p	r	p	r	p
MPV	0.166	0.381	0.260	0.165				
Age	−0.272	0.146	−0.163	0.390	−0.325	0.080	0.027	0.889
HbA1c	0.046	0.811	−0.045	0.814	−0.165	0.385	−0.032	0.867
TC	- 0.528	0.005*	- 0.534	0.002*	−0.055	0.771	0.103	0.588
TGs	−0.111	0.560	0.237	0.207	0.080	0.674	0.149	0.431
HDL	0.077	0.687	−0.190	0.316	0.032	0.865	−0.205	0.278
LDL	0.041	0.831	0.178	0.347	0.130	0.494	0.114	0.547
Urea	0.434	0.017*	0.922	0.001*	0.055	0.774	0.168	0.375
Creatinine	0.368	0.045*	0.798	0.001*	−0.051	0.787	−0.321	0.053
eGFR	- 0.505	0.004*	- 0.807	0.001*	0.064	0.738	0.318	0.061
CRP	0.407	0.026*	0.764	0.001*	0.012	0.950	−0.307	0.099
Hb%	−0.625	0.001*	- 0.759	0.001*	0.225	0.232	0.150	0.428
PLT	−0.127	0.503	−0.041	0.828	0.055	0.771	0.060	0.754
Neutrophil	0.249	0.184	0.434	0.017*	0.024	0.899	0.341	0.052
Lymphocyte	−0.787	0.001*	−0.424	0.019*	−0.141	0.458	0.326	0.079
UAE	0.428	0.001*	0.745	0.001*	−0.151	0.427	−0.301	0.106
FBG	−0.016	0.932	0.301	0.106	−0.124	0.515	0.033	0.862
PPS	−0.105	0.580	0.178	0.348	−0.076	0.691	0.067	0.725
ESR1	0.279	0.135	−0.069	0.718	−0.148	0.434	−0.147	0.357
ESR2	0.346	0.061	−0.182	0.335	−0.131	0.489	−0.354	0.055

* Significant ($p < 0.05$).

Table 5
ROC curve of NLR and MPV.

Data	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
NLR	0.980	96	91	93	95	94
MPV	0.621	76	66	72	70	72

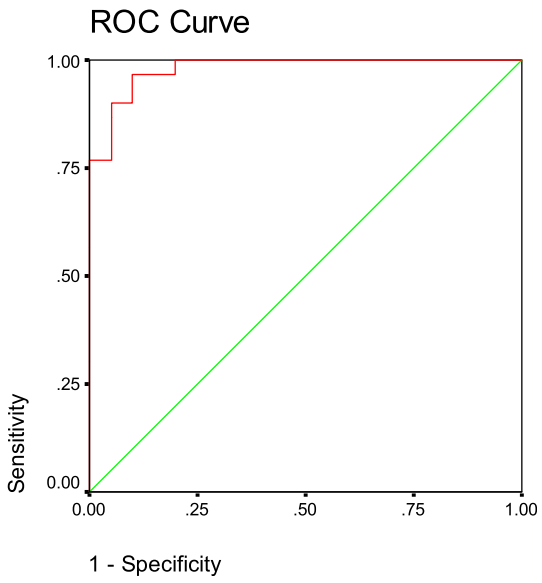

Fig. 1. ROC for NLR

similar to the results reported by Kodiatte et al., 2012 [20] and Demirtunc et al., 2010 [21]. Their studies showed that in diabetes mellitus, platelets become more reactive and aggregable and their MPV is increased. The increased platelet size may be one factor in the increased risk of atherosclerosis associated with DM and associated vascular complications. The present study showed higher MPV values for the diabetics and DN patients, when compared to controls, but with no significant difference. That was partially in accordance with the results of Alhadas et al. (2016) [15]

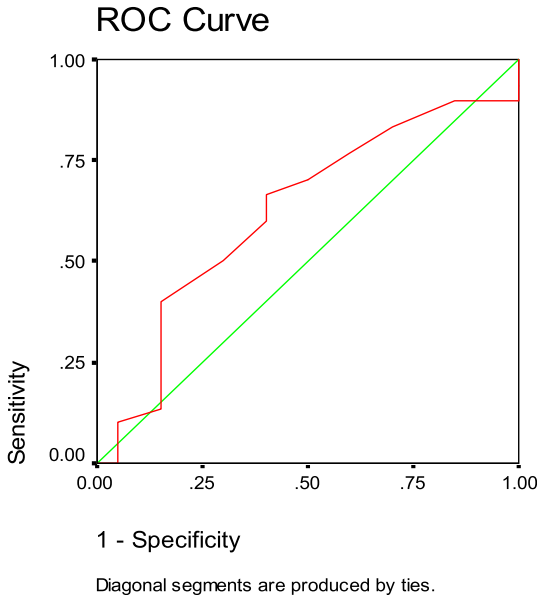

Fig. 2. ROC for MPV

where the mean MPV was significantly higher in the diabetic group compared to the controls. On the other hand, in a study by Zuberi et al. (2008) [22] MPV was significantly higher in diabetic patients with vascular complications than in diabetics without complications.

Although the underlying mechanism of high MPV in diabetics is not completely understood, it has been suggested that increased MPV in diabetes may be due to osmotic swelling of the platelets or due to the effect of insulin, which forces megakaryocytes to produce platelets with large sizes. Another postulated theory may reflect increased platelet turnover and increased presence of younger thrombocytes [23].

Several authors have suggested that patients with T2DM have increased MPV when compared with non-diabetic, and among the diabetics, those with vascular complications presented higher MPV values [24]. In the current study there was a significant increase in neutrophil count in-patient groups especially DN group ($P = 0.001$), that agreed with Xu et al. (2017) [25].

Lymphocyte showed a significant increases in patient groups especially DN group ($P = 0.001$), this disagreed with the study done by Moursy et al. (2015) [18] who found no significant difference between patients with type 2 diabetes, and patients with one or more microvascular complication as regard to lymphocyte. While our result was in accordance with that of Tsai et al. (2007) [26]. The biological mechanisms by which leucocytes and their subtypes play a role in mediating increased protein and albumin excretion is not fully known. Leucocytes play an important role in the initiation and progression of renal disease, by inflammatory mechanisms independent of infection. It was shown that leucocytes cause proteolysis and oxidative damage to the mesangial cells [27]. In this work, NLR levels were significantly higher in patients with DN than among diabetic patients and control group ($p < 0.001$), that was in accordance with the results reported in the studies performed by (Moursy et al., 2015 [18], and Huang et al., 2015) [10]. Afsar et al. (2014) [28] have shown that NLR could be related to the presence of diabetic nephropathy and it has been correlated as an indicator of end stage renal disease.

Some studies have shown that DM patients with DN, albuminuria or macroalbuminuria have higher NLR, compared with those without DN, albuminuria or with microalbuminuria, which indicated that NLR plays an important role in the development and progression of DN [16]. In our study there was a significant negative correlation between NLR and GFR in diabetic group ($P = 0.004$)and in DN group ($P = 0.001$), that agreed with Liu et al. (2018) [16] who stated that NLR, as a novel inflammation marker, is inversely associated with GFR patients with chronic kidney disease. A three-year follow-up study by Azab et al. (2012) [29] showed that NLR could serve as a predictor of worsening renal function in diabetes patients.

There was a significant positive correlation between NLR and CRP with in diabetic group ($P = 0.026$) and in DN group ($P = 0.001$), that agreed with several studies (Okyay et al., 2013 [30] and Kahraman et al., 2016) [31]. In the present study, ROC was done for NLR and showed 96% sensitivity, 91% specificity, 93% positive predictive value, 95% negative predictive value and 94% accuracy. Up to our knowledge, the ROC was not performed in any previous studies and our study is the first one to evaluate the sensitivity, specificity and predictive values of NLR in early detection of DN. Also, our study was the first study in which the ROC was done for MPV and showed 76% sensitivity, 66% specificity, 72% positive predictive value, 70% negative predictive value and 72% accuracy.

6. Conclusion

NLR was significantly higher in patients with DN and correlated

significantly with the renal function and UAE. Therefore, use of NLR is an easy, bedside and cheap method in early prediction of DN and can be evaluated by a simple blood count. MPV was of no significant value in prediction of diabetic nephropathy.

7. Limitations

Small number of patients (n = 60).

8. Recommendation

More studies needed on large number of patients to focus on NLR and its relation to other methods for assessment of patients with early diabetic nephropathy. Regular follow up by NLR for diabetic patients may be beneficial taking in consideration that it is cheap bedside test. Also, more evaluation of the role of MPV in DN is needed.

Conflicts of interest

The authors declare no conflicts of interest.

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