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Monocyte lymphocyte ratio, IL 6, and their association with increased carotid intima-media thickness as simple predictive markers for nephropathy in Egyptian diabetic patients

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Abstract

Background Inflammation is a cardinal mechanism of diabetic kidney disease (DKD). Interleukin-6 (IL6) is a reliable indicator that plays a role in the progression of DKD. Monocyte-to-lymphocyte ratio (MLR) is also implicated in this inflammatory process. The progression of DKD is associated with increased carotid intima-media thickness (CIMT), which is an independent predictor of atherosclerosis.

Aim The role of IL6 and MLR ratio influencing the progression of DKD was assessed using the urinary albumin creatinine ratio (UACR) and glomerular filtration rate (GFR). Moreover, their contribution to increasing CIMT in DKD was assessed.

Methods An observational prospective study was conducted on ninety diabetic patients presented to the Internal Medicine Clinic at Kasr AlAiny. The subjects were classified into three groups, thirty patients for each, according to UACR: with normoalbuminuria, microalbuminuria, and macroalbuminuria. A history and clinical assessment, CBC, MLR, HbA1c, lipid profile, IL6, creatinine, and eGFR were carried out. Furthermore, CIMT was measured using Doppler ultrasound.

Results The results showed that IL6 and MLR were significantly higher in the macroalbuminuria group compared to the other two groups with $p < 0.001$, suggesting that their higher level could predict the progression of DKD. According to the ROC curve, the cutoff values of MLR and IL6 were 0.3425 and 7 pg/ml, respectively. Moreover, CIMT increased significantly in micro and macroalbuminuric patients with $p > 0.001$. IL6 and MLR were positively correlated with CIMT in micro and macroalbuminuric patients.

Conclusion Both MLR and IL-6, as simple biomarkers associated with increased CIMT, play an important role in predicting the nephropathy of DKD patients.

Keywords DKD, Albuminuria, eGFR, MLR, IL-6, CIMT

Introduction

Diabetic kidney disease is one of the most prevalent major causes of renal disease that progresses to end-stage kidney disease and necessitates ongoing hemodialysis [1]. Thus, the early detection of the risk for diabetes and microvascular complications offers a chance to implement prophylactics to halt or postpone the onset of the

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disease and its progression. Interleukin (IL)-6 is a proinflammatory cytokine secreted by all types of kidney cells, podocytes, and mesangial cells, as well as endothelial and epithelial cells [2]. It can stimulate the release of other cytokines [3]. So IL-6, as a significant inflammatory mediator, is thought to be involved in the pathophysiology of DKD [4]. Furthermore, low lymphocyte counts and high monocyte counts have been used as inflammatory markers in several studies, and it has been suggested that they may be used in the diagnosis or estimation of prognosis in inflammatory states for DKD patients [5].

Diabetes is well known to be a risk factor for atherosclerotic diseases. So, CIMT measurement permits the early identification of arterial wall atherosclerotic lesions [6]. To promote atherogenesis, IL-6 is reported to stimulate monocyte chemoattractant protein 1 secretion from macrophages [3] and is associated with the increased expression of cell adhesion molecules [7]. Moreover, it was discovered that increased MLR resulted in an imbalance in innate and adaptive immunity. This imbalance may be the main cause of increased CIMT and atherosclerotic plaque formation [8].

Objectives

The aim of this study is to detect the role of MLR as a marker of inflammation and IL6 as a proinflammatory cytokine, which are associated with the development and progression of DKD assessed by UACR and eGFR. Additionally, assessing the impact of elevated levels of IL 6 and MLR on CIMT in DKD patients.

Methods

Our observational prospective study was conducted on ninety diabetic patients presented to our Internal Medicine Clinic at Kasr Al-Ainy from December 2022 to July 2023. Based on UACR, the subjects were divided into three groups: thirty diabetic patients for each group: normoalbuminuria (< 30) (without nephropathy), microalbuminuria (30–300), and macroalbuminuria (> 300). In accordance with current KDIGO guidelines 2020, CKD is defined as persistently elevated urine albumin creatinine excretion (≥ 30 mg/g, persistently reduced estimated glomerular filtration rate (eGFR < 60 ml/min per 1.73 m^2), or both for 3 months. Patients were fully informed about the research plan, and consent was obtained from every patient. A full history was taken for each subject, and a clinical assessment was carried out. UACR, complete blood count with an assessment of MLR, HbA1c, lipid profile, serum creatinine, and GFR were calculated by the chronic kidney disease epidemiology collaboration (CKD EPI) equation, and IL6 was conducted. Type II diabetic patients with an average age of 40–60 years and normal thyroid function met the inclusion criteria. Patients with uncontrolled hypertension, smokers, or those with autoimmune, cancer, infection, or inflammatory conditions were excluded.

A Philips ultrasound system with a 5–10-MHz multifrequency high-resolution linear transducer (L9–12) was used to perform automated measurements of CIMT in mm. The measurements were carried out in the longitudinal section of the common carotid artery (CCA). CIMT was measured at a distance of at least 5 mm below the distal end of CCA before the carotid bifurcation [9] with the subject lying down, neck extended and head slightly turned in the direction opposite to the carotid artery being examined at the posterior wall, along an axis perpendicular to the artery, to establish a line from the intima to media interface. The averaged CIMT of the maximum value on both sides was calculated as follows: CIMT = (Right-CIMT + Left-CIMT)/2. CIMT values between 0.5 and 0.8 mm were considered to be within the normal range [10] (Fig. 1). The approval number of the ethical committee was MS-261–2022.

Statistical analysis

According to this equation for calculating the sample size: Qualtrics = (Zscore)2 × StdDevx(1-StdDev)/(margin of error)2. After converting the confidence level to the Z score, assuming a confidence level of 95%, the *Z* score = 1.96, and a margin of error (confidence interval) of 10%. Therefore, the final sample size was 96 participants.

Data were coded and entered using the Statistical Package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). They were summarized using mean and standard deviation for normally distributed quantitative variables or median and interquartile range for non-normally distributed quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were made using analysis of variance (ANOVA) with multiple comparisons post hoc test in normally distributed quantitative variables, while non-parametric Kruskal–Wallis test and Mann–Whitney test were used for non-normally distributed quantitative variables [11]. The chi-square ((2) test was performed to compare categorical data. The exact test was used when the expected frequency was less than 5 [12]. Correlations between quantitative variables were conducted using the Spearman correlation coefficient [13]. The receiver operating characteristic curve (ROC curve) was constructed with the area under curve analysis performed to detect the best cutoff value of IL-6 and MLR to detect albuminuria. *P*-values less than 0.05 were considered statistically significant.

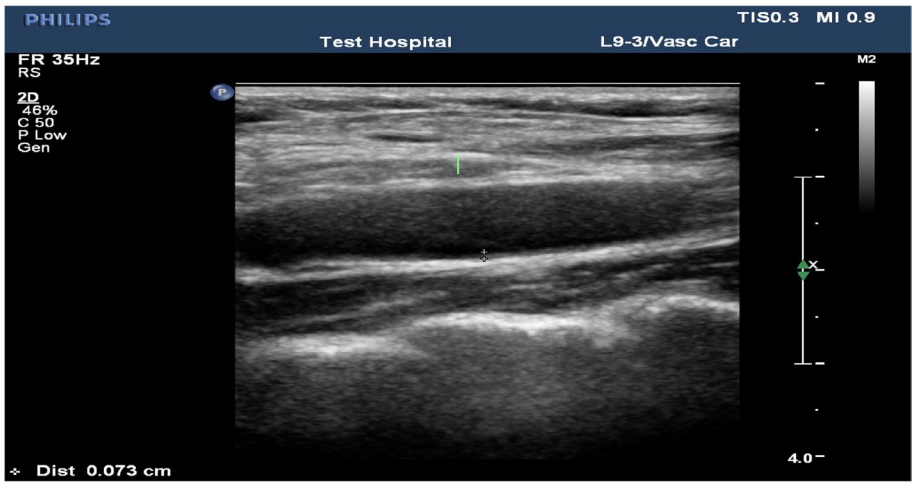


Fig. 1 Measurement of CIMT

Table 1 Demographic data of the studied groups

	Normoalbuminuric group	Microalbuminuric group	Macroalbuminuric group	*P*-value
	Count	Count	Count	
Sex				
Female	16	17	18	0.873
Male	14	13	12	

Results

The study was performed with 96 diabetic patients, but six patients were excluded due to suspected underlying malignancy and infection. The number of female patients was 16 in the normoalbuminuric group, 17 in the microalbuminuric group, and 18 in the macroalbuminuric group. The number of male patients was 14 in the normoalbuminuric group, 13 in the microalbuminuric group, and 12 in the macroalbuminuric group. The analysis indicated no statistically significant difference in the distribution of sex and BMI among the three groups. The mean age was 49 in the normoalbuminuric group, 51.27 in the microalbuminuric group, and 50.47 in the macroalbuminuric group. It had no statistically significant difference among the three groups, with a *P*-value of 0.0531. The participant demographic distribution is presented in Tables 1 and 2.

LDL and TG mean was 72.76 mg/dl and 117.97 mg/dl, respectively, in the normoalbuminuric group, 84.63 mg/dl and 140.27 mg/dl, respectively, in microalbuminuric group and 113.50 mg/dl and 218.33 mg/dl, respectively, in macroalbuminuric group mg/dl. Both LDL and TG showed statistically significant differences among the three groups ($p < 0.001$) (Table 2 and Fig. 2a, b). On the other hand, cholesterol showed no statistically significant difference

Table 2 Demographic data and laboratory data of the studied groups

	Normoalbuminuric group		Microalbuminuric group		Macroalbuminuric group		*P*-value	Effect size
	Mean	SD	Mean	SD	Mean	SD		
Age	49.00	8.56	51.27	7.57	50.47	7.47	0.531	0.014
BMI	31.79	7.27	34.30	7.52	34.39	7.24	0.304	0.027
Cholesterol	184.93	36.56	190.47	39.99	207.87	52.25	0.109	0.050
TG	117.97	57.89	140.27	67.54	218.33	99.80	< 0.001	0.243
HDL	50.33	19.82	53.70	17.08	49.97	28.01	0.772	0.006
LDL	72.76	34.05	84.63	28.44	113.50	52.48	< 0.001	0.161
HbA1C	7.47	1.04	9.02	1.72	11.10	1.51	< 0.001	0.521
Creatine	0.85	0.28	1.12	0.46	2.18	1.60	< 0.001	0.266
eGFR	98.90	22.62	78.63	29.13	46.17	25.28	< 0.001	0.423
MLR	0.25	0.14	0.26	0.16	0.48	0.15	< 0.001	0.332
IL6	4.81	7.16	16.74	7.74	29.40	5.74	< 0.001	0.684

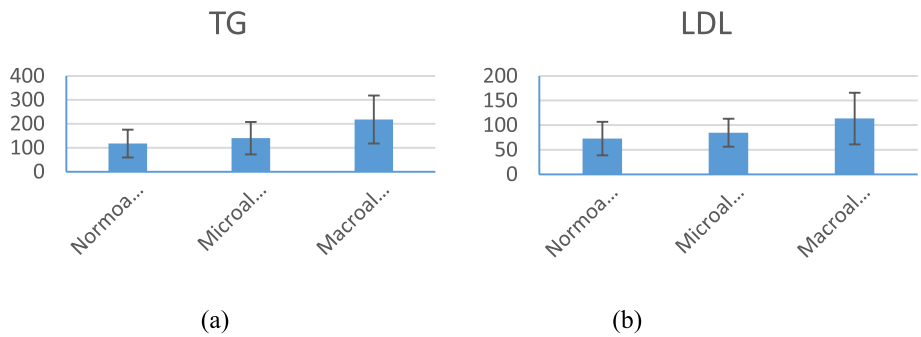


Fig. 2 **a**, **b** Comparison between the studied groups regarding triglycerides (TG) and LDL

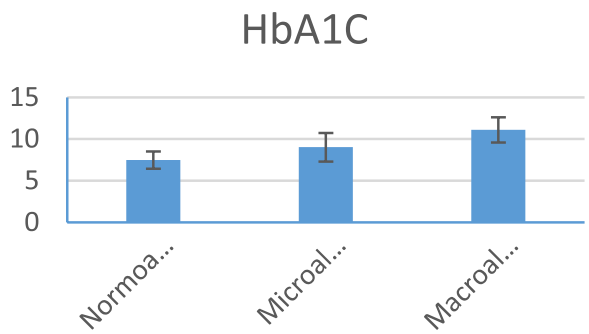


Fig. 3 Comparison between the studied groups regarding HbA1c

among the three groups. Our study revealed that the HbA1C mean was 7.47 in the normoalbuminuric group, 9.02 in the microalbuminuric group, and 11.10 in the macroalbuminuric group. HbA1c was significantly elevated in the macroalbumiuric group compared to the normo and microalbuminuric groups ($p < 0.001$) (Table 2, Fig. 3).

Creatinine and eGFR mean were 0.85 mg/dl and 98.90 mL/min, respectively, in the normoalbuminuric group, 1.12 mg/dl and 78.63 ml/min, respectively, in the microalbuminuric group, and 2.18 mg/dl and 46.17 ml/min, respectively, in the macroalbuminuric group.

MLR and IL6 mean were 0.25 and 4.81 pg/ ml, respectively, in the normoalbuminuric group, 0.26 and 16.74 pg/ml, respectively, in the microalbuminuric group, and 0.48 and 29.40 pg/ml, respectively, in the macroalbuminuric group. Both MLR and IL6 showed a statistically significant difference in the macroalbuminuric group compared to the other two groups ($p < 0.001$) (Table 2, Fig. 4a, b).

CIMT mean measures among the three groups were 0.08 mm in the normoalbuminuric group, 0.64 mm in the microalbuminuric group, and 0.95 mm in the macroalbuminuric group, as shown in Table 3 and Fig. 5. It was significantly higher in the macroalbuminuric group than in the normoalbuminuric and microalbuminuria groups ($p < 0.001$).

As demonstrated in Tables 4 and 5, MLR exhibited a significant positive correlation with CIMT among micro and macroalbuminuric groups of DKD patients (*P*-value 0.045) in the microalbuminuric group and *P*-value 0.024 in the macroalbuminuric group. IL6 had a significant positive correlation with CIMT among micro and macroalbuminuric groups of DKD patients (*P*-value 0.021) in the microalbuminuric group and *P*-value 0.025 in the macroalbuminuric group (Fig. 6a, b).

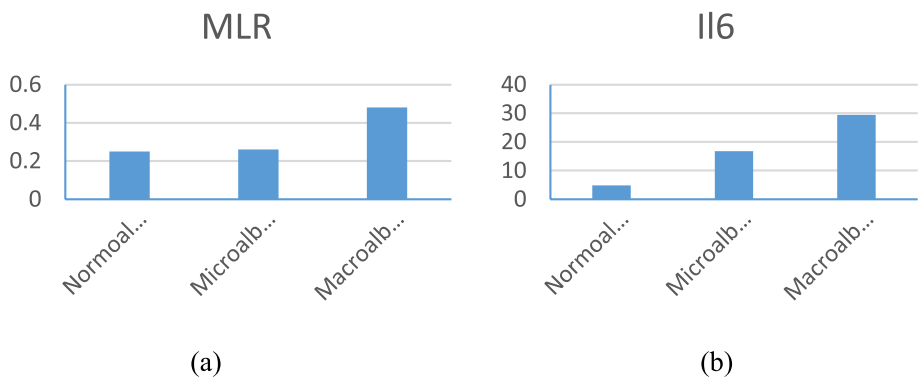


Fig.4 **a**, **b** Comparison between the studied groups regarding MLR and IL6

Table 3 CIMT measures of the studied groups

	Normoalbuminuric group		Microalbuminuric group		Macroalbuminuric group		*P*-value
	Mean	SD	Mean	SD	Mean	SD	
CIMT	0.08	0.01	0.64	0.17	0.95	0.12	< 0.001

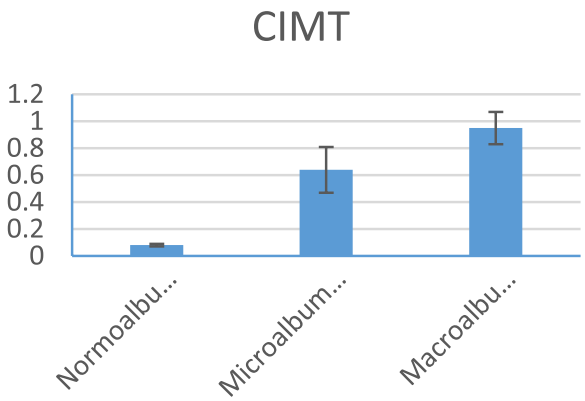


Fig. 5 Comparison between the studied groups regarding CIMT

MLR and IL-6 exhibited a significant positive correlation in diabetic patients with (*P*-value < 0.001), as shown in Table 6 and Fig. 7.

The ROC curve was constructed to assess the best cutoff values of MLR between the three studied groups. It revealed an AUC of 0.694 and a cutoff level of 0.3425, with a sensitivity of 58.3% and a specificity of 76.7%. On the other hand, the ROC curve described the best cutoff values of serum IL6 between the studied groups. It revealed an AUC of 0.929 and a cutoff level of 7 pg/ml, with a sensitivity of 93.3% and a specificity of 83.3%, as shown in Table 7 and Fig. 8.

Table 5 Correlation between MLR, IL 6, and CIMT with a total of ninety patients

		CIMT
CIMT	**Correlation coefficient**	1.000
	***P*-value**	
	N	90
MLR	**Correlation coefficient**	0.551
	***P*-value**	< 0.001
	N	90
IL6	**Correlation coefficient**	0.760
	***P*-value**	< 0.001
	N	90

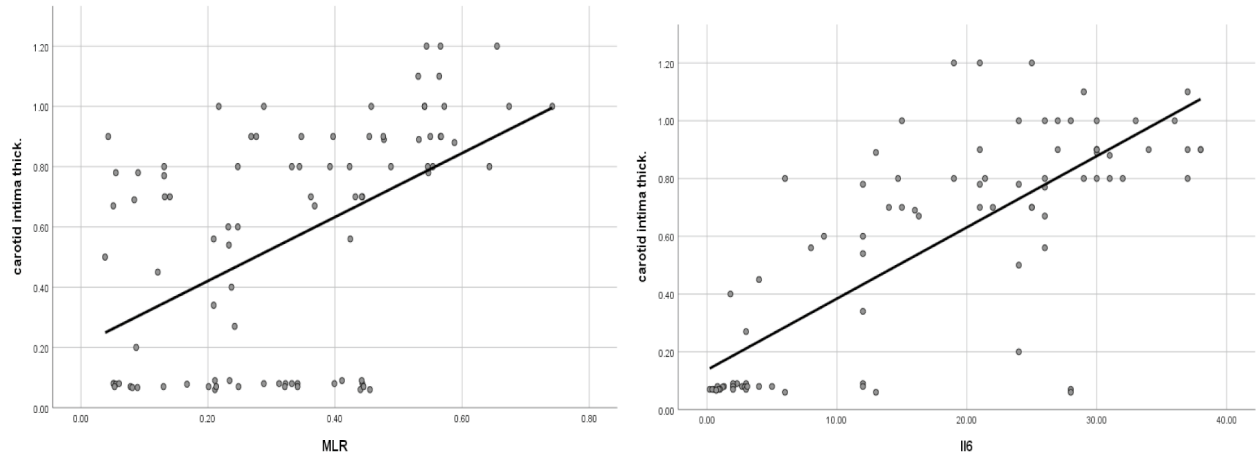
Discussion

In this study, we investigated the association between IL6 and MLR, which could be involved in multiple inflammatory pathways leading to the development of DKD and its progression. Albuminuria is considered an early stage for diabetic nephropathy.

Interleukin-6 (IL-6) is an important pro-inflammatory cytokine contributing to the onset and acceleration of microvascular and macrovascular complications in diabetes patients [14]. Overexpression of IL6 and its receptor can be mediated by podocytes, which may play a role in the development of various glomerular diseases. Moreover, Kim DI et al. found that elevated glucose induces IL-6 signal transduction and enhances IL-6 secretion in podocytes [15]. Furthermore, mesangial cells also have the ability to secrete IL-6, which stimulates the mesangial cells to produce monocyte chemoattractant protein 1,

Table 4 Correlation between MLR, IL 6, and CIMT among the groups

		Normoalbuminuric group	Microalbuminuric group	Macroalbuminuric group
		CIMT	CIMT	CIMT
CIMT	**Correlation coefficient**	1.000	1.000	1.000
	***P* value**			
	N	30	30	30
MLR	**Correlation coefficient**	0.084	0.369	0.411
	***P* value**	0.659	0.045	0.024
	N	30	30	30
Il6	**Correlation coefficient**	0.152	−0.420	−0.408
	***P* value**	0.423	0.021	0.025
	N	30	30	30



(a) (b)

Fig. 6 **a**, **b** Scatterplot showing a positive correlation between CIMT, MLR and IL6

Table 6 Correlation between MLR and IL 6

		MLR
IL6	**Correlation coefficient**	0.545
	***P*-value**	< 0.001
	N	90

which in turn increased monocyte recruitment and plays an important role in kidney injury [16]. Recently, it was found that IL-6 gene polymorphism is an independent risk factor for DKD in type II diabetic patients [17]. MLR is another inflammatory marker that was found to be a highly accurate predictor of diabetic nephropathy [14].

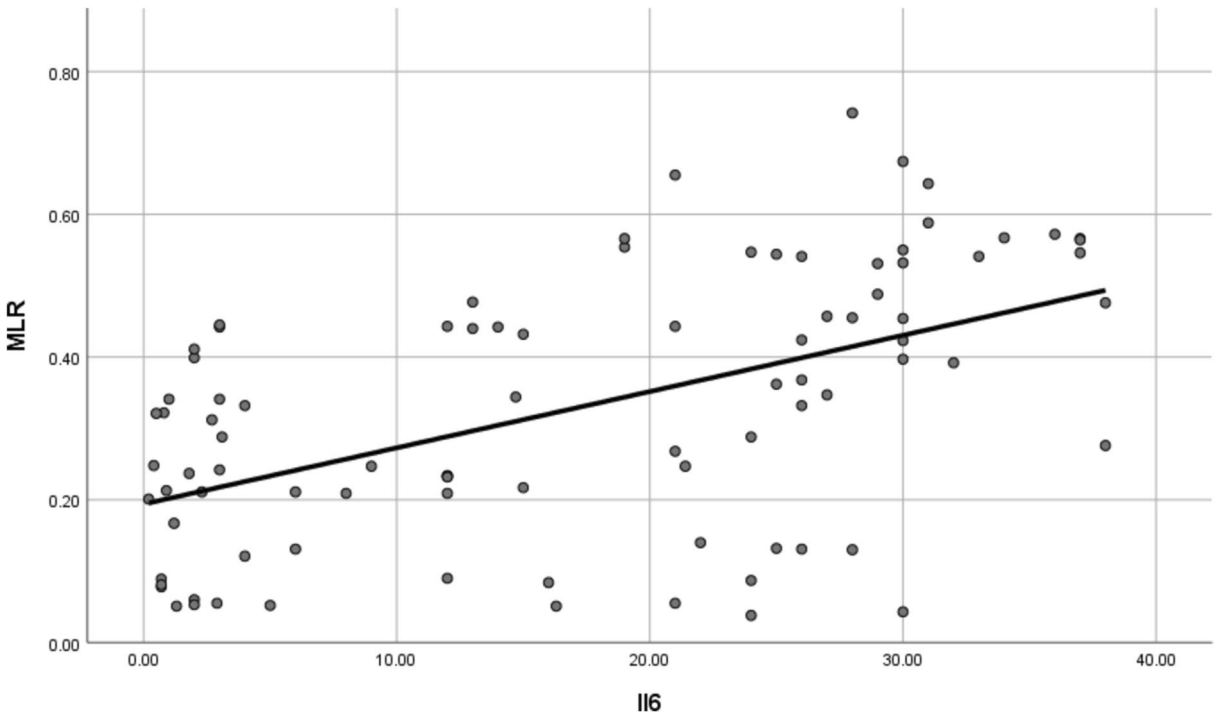


Fig. 7 Scatterplot showing a positive correlation between MLR and IL-6

Table 7 Cutoff value for the detection of proteinuria using IL-6 and MLR

	Area under the curve	*P* value	95% confidence interval		Cut off	Sensitivity %	Specificity %
			Lower bound	Upper bound			
MLR	0.694	< 0.001	0.587	0.801	0.3425	58.3	76.7
Il6	0.929	< 0.001	0.865	0.993	7	93.3	83.3

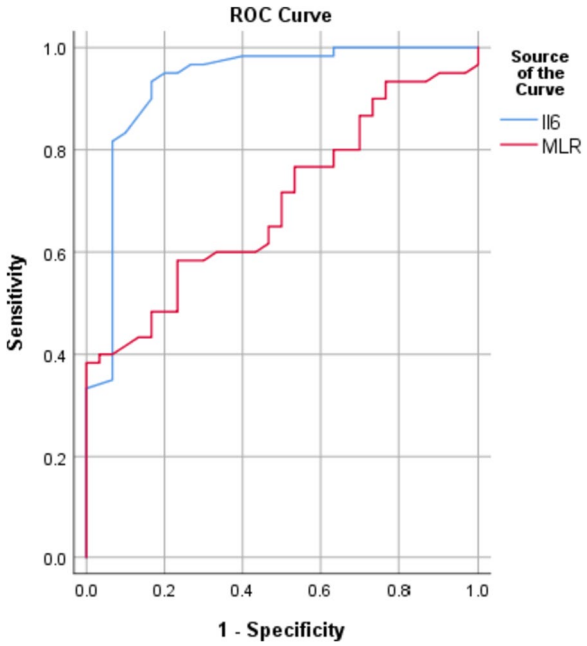


Fig. 8 ROC curve for detection of the cutoff of IL6 and MLR

The current study revealed a statistically significant difference in IL6 levels and MLR among the three groups, which are significantly higher in the macroalbuminuria group compared to the other two groups with a (p-value < 0.001), suggesting that the rising levels of IL6 and MLR in the micro and macroalbuminuric group in diabetic patients may have an important role in the inflammatory process which are associated with development and DKD progression. To further evaluate the predictive value of MLR for DKD risk, a ROC curve analysis was carried out. As described earlier, the ROC curve illustrated the cutoff values of serum IL6 and MLR between the studied groups, which were 7 pg/ml and 0.3425, respectively Fig. 7 with a sensitivity of 58.3% and a specificity of 76.7% for MLR and a sensitivity of 93.3% and a specificity of 83.3% for IL6.

Our results agreed with Pham et al., who found a significant positive correlation between serum IL-6 and UACR in diabetic patients with UACR ≥ 30 mg/g [18]. Furthermore, Akihiko et al. concluded that the level of IL6 was higher in participants with UACR > 30 mg/g or eGFR < 60 mL/min/1.73 m^2 compared with those with UACR < 30 mg/g or eGFR > 60 mL/min/1.73 $m^2 P < 0.01$ [19]. Similar to our study, Vaishya et al. found that the level of 24-h urinary protein was positively correlated with IL6 levels $P < 0.01$ [20]. On the other hand, in support of the study of Kocak et al., who reported that MLR was significantly and positively correlated with the microalbuminuria group of DKD patients [14]. Also, Mehmet Z et al. suggested that MLR could be a predictive marker for DKD due to its strong positive correlation with microalbuminuria [5].

Microalbuminuria has been extensively regarded as a marker of endothelial dysfunction. There is also a pathophysiological mechanism linking albuminuria to atherosclerosis, which is related to its inflammatory role [21]. Our analysis emphasized the significant correlation between CIMT and albuminuria, and this result suggests that as DKD progresses from microalbuminuria to macroalbuminuria, there is a corresponding increase in CIMT. Ersin et al. observed a significant increase in CIMT in diabetic microalbuminuric patients with a P-value < 0.0001 [22].

In our study, the analysis showed a statistically significant difference in IL6 levels and MLR with increased CIMT in the microalbuminuric and macroalbuminuric groups compared to the normoalbuminuric group. Patients with increased CIMT had a higher level of IL6 and MLR, which may indicate an ongoing inflammatory process and a possible correlation with CIMT abnormalities. This coincides with the findings of Yu-qing et al., who found a positively correlated CIMT with IL-6 with a P-value < 0.001 [23]. According to Gong et al., MLR might be a more reliable predictor of atherosclerosis risk, identified early through CIMT evaluation [24]. Moreover, Sah Bandar et al. found that higher circulating monocytes were correlated with common carotid artery intima-media thickness [25].

Limitations

(I) Selecting patients who met these exclusion criteria was challenging. (II) Merely taking single measurements of MLR and IL6 may not be sufficient to detect variations in these parameters. (III) Anti-diabetic drug's effect on IL6 and MLR levels was not obviously detected.

Recommendations

As MLR and IL6 markers are simple and readily available, we recommend using them in daily practice, like the calculation of eGFR, as they might help in the early detection and follow-up of DKD patients to assess the ongoing inflammatory process of DKD which is associated with their higher level among DKD patients. Additionally, we recommend conducting studies with trials of anti-IL6 antibodies, which may halt the progression of DKD.

Conclusion

We suggest that MLR, IL6, and their association with increased CIMT could serve as a predictive marker for nephropathy in diabetic subjects due to its strong correlation with albuminuria. It may serve as an estimation of the underlying inflammatory burden that promotes nephropathy in diabetic subjects.

Abbreviations

MLR	Monocyte-to-lymphocyte ratio
IL6	Interleukin-6
CIMT	Carotid intima-media thickness
CCA	Common carotid artery
CKD EPI	Chronic kidney disease Epidemiology Collaboration equation
DKD	Diabetic kidney disease
ROC curve	Receiver operating characteristic curve
UACR	Urinary albumin creatinine ratio
eGFR	Estimated glomerular filtration rate
BMI	Body mass index
TG	Triglycerides
KDIGO	Kidney Disease: Improving Global Outcomes

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Authors' contributions

Heba Mahmoud helped choose the research topic, used Doppler ultrasonography to evaluate CIMT, reviewed this study, wrote the discussion, and wrote this paper. Prof Heba Morad reviewed every detail in the study and made an effort to fix any mistakes. Dr Deena Sharshar contributed to collecting samples, contributed to writing the research, and played a role in funding this research. Prof Tarek Ramzy provided us with laboratory results.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Consent for publication

There was no individual person's data in any form (including individual details, images, or videos).

Competing interests

I, the corresponding author, confirm on behalf of all authors that there have been no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated. We have no conflict of interest to disclose.

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