ORIGINAL ARTICLE

Comparison of complete blood count parameters in different severity of proteinuria among patients with type 2 diabetes mellitus

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Background: Proteinuria is a key indicator of kidney damage in diabetic nephropathy, and its severity correlates with the progression of the disease. In diabetic patients, it is crucial to identify reliable predictors for proteinuria and its severity for early detection and management of kidney damage. **Materials and Methods:** This cross-sectional study was conducted from November 16, 2022, to May 20, 2023, on patients with type 2 diabetes mellitus (T2DM) who were outpatients at clinics of Shahid Modarres Hospital, Tehran, Iran. Participants were categorized based on their level of proteinuria during 24-h as follows: group A1 (normal to mildly increased proteinuria), Group A2 (moderately increased proteinuria), and Group A3 (severely increased proteinuria). Then, complete blood cell count and other laboratory parameters, were compared between study groups. **Results:** In this cross-sectional study, 128 participants, including 53 (41.4%) men and 75 (58.6%) women with T2DM, were enrolled. The mean age of participants was 56.40 ± 13.31 years. Although there were no significant differences between cell count and parameters of three groups, a statistically significant difference was seen in neutrophil-to-lymphocyte ratio (NLR) (1.93 ± 0.76, 2.34 ± 0.93, and 2.73 ± 1.07 in A1, A2, and A3 groups, respectively; $P = 0.003$). Further analysis showed that NLR was significantly higher in Group A3 compared to A1 (2.73 ± 1.07 vs. 1.93 ± 0.76, respectively; $P = 0.006$), but there was no significant difference between Groups A3 and A2 (2.73 ± 1.07 vs. 2.34 ± 0.93, respectively; $P = 0.482$) and between Groups A2 and A1 (2.34 ± 0.93 vs. 1.93 ± 0.76, respectively; $P = 0.257$). **Conclusion:** Overall, this study suggests that some routine laboratory parameters may be associated with proteinuria and its severity in patients with T2DM. NLR, in particular, showed this association in our study, promising future studies evaluating this association and whether it can help as a predictor or not.

Key words: Blood cell count, diabetes mellitus, lymphocytes, neutrophils, proteinuria

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INTRODUCTION

Diabetes mellitus is a widespread chronic disease characterized by high blood glucose levels due to impaired insulin secretion or resistance; type 2 diabetes mellitus (T2DM) being far more common.[1] It is a significant public health concern, affecting millions of people worldwide.[1] In addition, recent studies have shown that its prevalence is increasing in Iran in the past few years.[2] The complications of T2DM, which are caused by chronic high blood sugar, form a set of systemic

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symptoms and involvements that have a significant impact on the patient and society's costs.[3] The greater importance of this issue is determined when these complications are imposed on patients in the active years of life, that is, middle age.[3] These complications include macrovascular complications such as coronary artery involvement, cerebral strokes, or peripheral vascular diseases, as well as microvascular complications including retinopathy, neuropathy, and nephropathy.[4] Diabetic nephropathy (DN) is a common complication of diabetes that affects the kidneys, leading to kidney damage and eventual kidney failure.[5] DN is one of the main causes of morbidity and mortality all over the world and imposes high costs on the health-care system of every country.[6] Proteinuria is a key indicator of kidney damage in DN, and its severity correlates with the progression of the disease.[7] Although the urinary albumin-to-creatinine ratio has been recommended for the evaluation of proteinuria, it has been reported to be more costly than alternatives as well as unreliable for estimating 24-h proteinuria in some clinical settings.[8] Moreover, a large cohort study showed that only 24% of patients with T2DM adhered to annually albumin-to-creatinine ratio testing and 25% never had a test.[9,10] Furthermore, the fluctuation and day-to-day variation of albuminuria has been reported in addition to its highly variability throughout the day.[11,12] On the other hand, the pathogenesis of DN is still not fully known, but evidence of inflammation and oxidative stress induced by hyperglycemia have been reported.[13] Despite the reported crucial role of inflammation in development of DN and its progression,[14] the high cost and difficulty in measurement of the inflammatory parameters and cytokines limit their application for routine clinical practice.[14] The identification of reliable predictors for proteinuria and its severity is crucial for early detection and management of kidney damage.[15] Therefore, several studies have investigated various routine laboratory biomarkers for this purpose, including the neutrophil-to-lymphocyte ratio (NLR).[16] The NLR is a simple and readily available marker of systemic inflammation that has been associated with the severity of various diseases.[17] Among complete blood count parameters, platelet-to-lymphocyte ratio has been also suggested for prediction of proteinuria.[16] Therefore, this study aims to compare the complete blood count parameters in different severity of proteinuria among patients with T2DM to find a potential simple and available laboratory parameter helping to predict proteinuria in this population.

METHODS

This cross-sectional study was conducted from November 16, 2022, to May 20, 2023, on patients with T2DM who were outpatients at the Nephrology or Endocrinology Clinics of Shahid Modarres Hospital, Tehran, Iran. This study was approved by Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1401.561). The study was carried out under the Declaration of Helsinki, written informed consent was obtained from all participants, and they were assured that all information would be confidential.

All patients aged more than 18 years with T2DM (fasting plasma glucose [FPG] ≥126 mg/dL or 2 h post 75 g glucose intake [2-h PG] ≥200 mg/dL during oral glucose tolerance test or HbA1C ≥6.5% or a random plasma glucose ≥200 in a patient with classic symptoms of hyperglycemia or taking any glucose-lowering medications[18]) for at least 5 years since diagnosis were included. Exclusion criteria consisted of stage 5 of chronic kidney disease (estimated glomerular filtration rate [eGFR] <15 ml/min/1.73 m^2), hematological diseases, pregnancy, chronic inflammatory diseases, hypothyroidism, COVID-19, and other infectious diseases. Demographic information, including age and sex, were documented. Then, a 24-h urine sample was obtained from all participants and parameters including 24-h urine creatinine (mg/day), 24-h urine volume (mL/day), and 24-h urine protein (mg/day) were measured. In addition, venous blood sample from antecubital vein was obtained following 12 h of fasting to assess FPG (mg/dl), glycated hemoglobin (HBA1c), serum creatinine (mg/dl), eGFR (ml/min/1.73 m^2), serum urea (mg/dl), uric acid (mg/dl), serum total cholesterol (mg/dl), high-density lipoprotein (mg/dl), low-density lipoprotein (mg/dl), serum triglyceride (mg/dl), aspartate aminotransferase (mg/dl), alanine aminotransferase (mg/dl), alkaline phosphatase (mg/dl), serum calcium (mg/dl), serum phosphorus (mg/dl), serum iron (μg/dl), total iron binding capacity (μg/dL), and complete blood cells count including absolute neutrophil count (ANC) ($x10^9$/L), absolute lymphocyte count (ALC) ($x10^9$/L), and NLR. All the patient's tests have been done in the same laboratory using the same method of analysis. Participants were categorized based on their level of proteinuria during 24-h as follows: Group A1 (normal to mildly increased proteinuria): <150 mg/24 h, Group A2 (moderately increased proteinuria): 150–500 mg/24 h, and Group A3 (severely increased proteinuria): >500 mg/24 h.[19] Then, NLR as well as other laboratory parameters, were compared between groups categorized based on their level of proteinuria during 24-h urine collection.

Statistical analysis

Quantitative results were presented as mean ± SD, and qualitative results were presented as frequency (percentage). The Kolmogorov–Smirnov test showed that all variables have a normal distribution, except for three variables, for which methods of evaluating and managing outlier data as well as transforming and standardizing non-normal data were used for normalization. Means were compared using

analysis of variance analysis. *Post hoc* analysis has been done in cases of significant differences between groups using the Scheffe test. The gender proportions between groups were compared using the Chi-squared test. $P < 0.05$ was considered statistically significant. SPSS statistical software package (SPSS, Inc., Chicago, IL, USA), version 22.0, and MedCalc software version 22.026 by Ostend, Belgium were used for statistical analyses.

RESULTS

In this cross-sectional study, 128 participants, including 53 (41.4%) men and 75 (58.6%) women with T2DM, were enrolled. The distribution of gender in study groups is shown in Table 1. The mean age of participants was 56.40 ± 13.31 years. After categorizing based on the level of proteinuria during 24-h urine collection, Group A1 (normal to mildly increased proteinuria) consisted of 96 (75.0%) participants, Group A2 (moderately increased proteinuria) 15 (11.7%), and Group A3 (severely increased proteinuria) 17 (13.3%) participants. The mean age of participants in each group is mentioned in Table 1; there was no significant difference between groups in terms of age and gender distribution ($P = 0.542$ and 0.247, respectively). In terms of glycemic control, the mean amount of HBA_1c and FPG in all participants was 7.07 ± 2.36 and 142.63 ± 74.36 mg/dl, respectively, which did not show any significant difference

Table 1: Comparison between demographic and laboratory findings (presented as mean±standard deviation) of participants categorized based on their level of proteinuria during 24-h urine collection

	Total (*n*=128)	A1 (normal to mildly increased proteinuria), *n*=96	A2 (moderately increased proteinuria), *n*=15	A3 (severely increased proteinuria), *n*=17	*P*
Age (years)	56.40±13.31	56.88±13.04	57.13±16.04	53.06±12.56	0.542
Gender:Male/female	53/75	36/60	7/8	10/7	0.247
24-h urine creatinine (mg/day)	681.60±489.53	616.37±487.92	880.05±550.10	856.03±379.02	0.054
24-h urine volume (mL/day)	1757.61±668.44	1679.69±634.19	1825.00±792.15	2018.75±677.47	0.181
24-h urine protein (mg/day)	231.65±479.38	45.51±39.77	245.79±78.09	1270.26±670.98	<0.001
Serum urea (mg/dL)	42.33±24.41	37.53±14.17	57.85±49.61	55.50±29.94	0.001
Serum creatinine (mg/dL)	1.37±0.72	1.19±0.43	1.90±1.44	1.93±0.78	<0.001
eGFR (mL/min/1.73 m^2)	61.07±23.51	65.44±21.13	50.09±26.79	45.70±25.45	0.001
FPG (mg/dL)	142.63±74.36	145.73±72.03	138.75±82.51	127.23±84.80	0.699
HBA_1c (%)	7.07±2.36	7.21±2.44	7.15±2.66	6.08±1.21	0.373
Uric acid (mg/dL)	4.87±1.52	4.64±1.36	4.98±1.56	6.02±1.90	0.007
Serum total cholesterol (mg/dL)	164.85±44.94	164.55±43.49	160.82±60.63	170.67±42.10	0.866
HDL (mg/dL)	46.97±10.67	47.77±11.24	43.70±6.09	43.38±8.55	0.324
LDL (mg/dL)	86.09±36.71	89.08±37.46	63.62±23.01	83.31±36.54	0.141
Serum triglyceride (mg/dL)	159.37±84.22	147.01±70.50	207.64±147.38	198.58±73.45	0.017
AST (mg/dL)	18.99±7.56	18.86±7.38	19.10±10.58	19.89±5.67	0.929
ALT (mg/dL)	22.00±10.43	21.52±9.87	24.60±16.57	22.89±6.11	0.663
ALP (mg/dL)	205.24±72.68	200.61±65.41	228.89±115.65	213.86±69.47	0.531
Serum calcium (mg/dL)	9.38±0.43	9.39±0.42	9.28±0.52	9.38±0.45	0.776
Serum phosphorus (mg/dL)	3.86±0.48	3.83±0.41	4.20±0.62	3.83±0.67	0.257
Serum iron (μg/dL)	71.85±26.91	74.26±24.79	37.00±26.32	75.00±29.74	0.024
TIBC (μg/dL)	323.98±61.49	325.00±55.57	348.75±118.22	307.78±64.75	0.534
WBC count (×10^9/L)	7.62±1.78	7.53±1.80	7.61±1.67	8.09±1.84	0.546
ANC (×10^9/L)	4.67±1.41	4.50±1.38	4.85±1.48	5.36±1.35	0.083
ALC (×10^9/L)	2.43±0.81	2.48±0.77	2.27±0.73	2.30±1.05	0.530
NLR	2.10±0.88	1.93±0.76	2.34±0.93	2.73±1.07	0.003
PLR	101.58±39.46	99.15±36.65	105.02±40.57	110.98±52.60	0.558
RBC count (×10^6/μL)	4.86±0.63	4.94±0.58	4.76±0.40	4.54±0.90	0.067
Hb (g/dL)	13.79±2.07	14.06±1.92	13.21±2.19	12.93±2.52	0.083
HCT (%)	42.26±5.03	42.92±4.50	41.16±4.77	39.88±7.00	0.068
MCV (fL)	87.37±6.63	87.35±6.81	86.44±7.09	88.37±5.39	0.738
MCH (pg)	28.53±3.06	28.68±3.16	27.66±3.39	28.58±2.10	0.526
MCHC (g/dL)	32.44±1.97	32.64±1.91	31.47±2.68	32.33±1.22	0.123
RDW (%)	13.87±1.38	13.77±1.39	14.45±1.39	13.85±1.29	0.242
Platelets count (×10^3/μL)	228.79±75.62	232.04±73.26	225.14±87.02	215.23±80.24	0.737

Hb=Hemoglobin; HBA_1c=Glycated Hb; eGFR=Estimated glomerular filtration rate; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; ALP=Alkaline phosphatase; TIBC=Total iron-binding capacity; WBC=White blood cell; ANC=Absolute neutrophil count; ALC=Absolute lymphocyte count; NLR=Neutrophil-to-lymphocyte ratio; PLR=Platelet-to-lymphocyte ratio; RBC=Red blood cell; HCT=Hematocrit; MCV=Mean corpuscular volume; MCH=Mean corpuscular Hb; MCHC=Mean corpuscular Hb concentration; RDW=Red cell distribution width; FPG=Fasting plasma glucose

between three groups of study [Table 1]. The 24-h urine and serum laboratory findings are mentioned in Table 1. The mean serum creatinine levels in Group A3 and A2 were significantly higher than Group A1 (1.93 ± 0.78 vs. 1.19 ± 0.43 mg/dl, $P < 0.001$ and 1.90 ± 1.44 vs. 1.19 ± 0.43 mg/dl, $P = 0.002$, respectively); but there was no statistically significant difference between Group A3 compared to A2 (1.93 ± 0.78 vs. 1.90 ± 1.44 mg/dl, respectively; $P = 0.995$). The mean level of eGFR was significantly lower in Group A3 compared to A1 (45.70 ± 25.45 vs. 65.44 ± 21.13 ml/min/1.73 m^2, respectively; $P = 0.006$), but there was no significant difference between Groups A3 and A2 (45.70 ± 25.45 vs. 50.09 ± 26.79 ml/min/1.73 m^2, respectively; $P = 0.871$) and between Group A2 and A1 (50.09 ± 26.79 vs. 65.44 ± 21.13 ml/min/1.73 m^2, respectively; $P = 0.074$). Among other serum laboratory markers, *post hoc* tests showed that the mean amount of serum urea in Group A1 was significantly lower than Group A2 (37.53 ± 14.17 vs. 57.85 ± 49.61 mg/dl, respectively; $P = 0.015$) and Group A3 (37.53 ± 14.17 vs. 55.50 ± 29.94 mg/dl, respectively; $P = 0.020$); but there was no statistically significant difference between Group A3 compared to A2 (55.50 ± 29.94 vs. 57.85 ± 49.61 mg/dl, respectively; $P = 0.964$). The mean serum uric acid level in Group A3 was significantly higher than Group A1 (6.02 ± 1.90 vs. 4.64 ± 1.36 mg/dl, respectively; $P = 0.007$), but it did not show any significant difference between Group A2 compared to A1 (4.98 ± 1.56 vs. 4.64 ± 1.36 mg/dl, respectively; $P = 0.789$) and Group A3 (4.98 ± 1.56 vs. 6.02 ± 1.90 mg/dl, respectively; $P = 0.235$). Among lipid profile parameters, the mean serum triglyceride level in Group A1 was significantly lower than Group A2 (147.01 ± 70.50 vs. 207.64 ± 147.38 mg/dl, respectively; $P = 0.023$) and Group A3 (147.01 ± 70.50 vs. 198.58 ± 73.45 mg/dl, respectively; $P = 0.044$); but there was no statistically significant difference between Groups A3 and A2 (198.58 ± 73.45 vs. 207.64 ± 147.38, respectively; $P = 0.791$). Among complete blood cell count findings, although there were no significant differences between cells count and parameters of three groups, a statistically significant difference was seen in NLR (1.93 ± 0.76, 2.34 ± 0.93, and 2.73 ± 1.07 in A1, A2, and A3 groups, respectively; $P = 0.003$) [Figure 1]. Further analysis showed that NLR was significantly higher in Group A3 compared to A1 (2.73 ± 1.07 vs. 1.93 ± 0.76, respectively; $P = 0.006$), but there was no significant difference between Groups A3 and A2 (2.73 ± 1.07 vs. 2.34 ± 0.93, respectively; $P = 0.482$) and between Groups A2 and A1 (2.34 ± 0.93 vs. 1.93 ± 0.76, respectively; $P = 0.257$). As mentioned in Table 1, other laboratory parameters did not have any significant differences between groups except for serum iron level (74.26 ± 24.79, 37.00 ± 26.32, and 75.00 ± 29.74 µg/dl in A1, A2, and A3 groups, respectively; $P = 0.024$), being lower in Group A2 (37.00 ± 26.32 µg/dl); which further analysis showed this difference being statistically significant only in comparison between Groups A2 and A1 (37.00 ± 26.32 vs. 74.26 ± 24.79 µg/dl, respectively; $P = 0.026$).

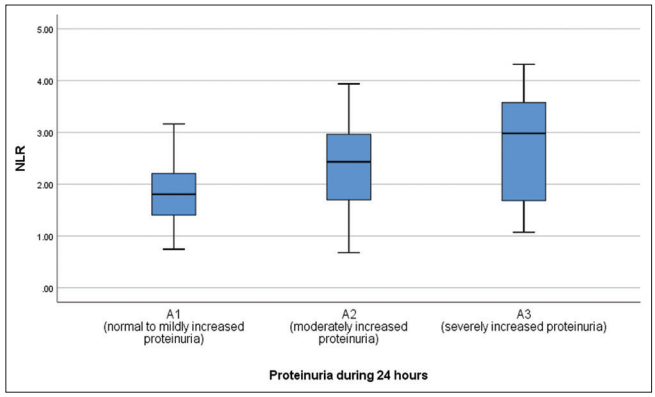

Figure 1: Comparison of neutrophil-to-lymphocyte ratio in different degree of proteinuria in diabetic patients.As can be seen in the graph, the median value of NLR is different in the three groups. Furthermore, in groups with higher levels of proteinuria (normal-mildly increased proteinuria to moderately increased and also moderately increased to severely increased proteinuria), the median value of NLR increases; with the highest median NLR belonging to the severe group. NLR: neutrophil to lymphocyte ratio

DISCUSSION

The findings of the present study showed that although there were no significant differences between blood cell count, especially white blood count (WBC) count, ANC, and ALC of the study groups, a statistically significant difference was seen in NLR based on the level of proteinuria in patients with T2DM. Further analysis showed that NLR was significantly higher in patients with severely increased proteinuria compared to patients with normal to mildly increased proteinuria, but there was no significant difference between patients with moderately and severely increased proteinuria, neither between patients with moderately and normal to mildly increased proteinuria.

Several previous studies have been published about the association of complete blood count parameters and proteinuria in patients with T2DM.[16,20-23] A study on patients with T2DM has reported a significant difference in NLR between patients with uncontrolled diabetes having microalbuminuria and patients without microalbuminuria, regardless of whether their diabetes was under control or not.[23] Moreover, among patients with uncontrolled diabetes, red cell distribution width (RDW) was significantly different between patients with and without microalbuminuria.[23] Another study reported exactly similar results.[22] However, in our study, NLR was significantly higher in patients with severely increased proteinuria than patients with normal to mildly increased proteinuria. Furthermore, we did not see any significant difference in RDW based on the level of proteinuria. It is worth mentioning that our study population had controlled diabetes and the glycemic control did not differ between study groups.

Another study used the urinary albumin-to-creatinine ratio for the assessment of albuminuria and their results

showed a significant correlation between increased NLR and PLR with DN.[16] Similarly, the results of another study in Ethiopia showed a significantly higher amount of mean NLR value in patients with DN compared to diabetic patients without DN.[21]

Some mechanisms have been suggested for explaining this issue. Although the major sign of DN development and its progression is the appearance of proteinuria, it appears that glomerular damage precedes this paraclinical clue.[24] In fact, the damage to the glomeruli results in the appearance of proteinuria, which itself worsens the inflammatory process and progressive renal damage, leading to renal fibrosis and dysfunction.[25] Therefore, various inflammatory mediators and cytokines have been suggested as contributors to DN development.[26] On the other hand, WBC counts and their subtype distribution, such as neutrophilia or lymphocytopenia, are known as inflammation markers and also independently associated with many clinical diseases, including DN.[27] Unlike neutrophils and lymphocyte count, which may be affected by different pathological or physiological conditions, NLR is more precise and includes both components of the innate and acquired immune systems by including both neutrophils and lymphocytes, respectively.[28]

Our study has several strengths. First, we categorized our participants based on proteinuria in the 24-urine sample and not a random urine sample. Second, the glycemic control did not have any significant difference between our study groups. Third, the other laboratory parameters, including a lipid profile, did not show any significant difference between our study groups, except for TG level. However, our study has several limitations as well; we did not measure the amount of albuminuria in 24-h urine. In addition, the present study was conducted as a single-center cross-sectional study with a limited number of participants. Future studies for the assessment of the value of NLR in the prediction of proteinuria are suggested.

CONCLUSION

This study suggests that some routine laboratory parameters may be associated with proteinuria and its severity in patients with T2DM. The association between NLR and proteinuria severity suggests that NLR can provide valuable information about the inflammatory status and kidney damage in diabetic patients which can propose the hypothetical potential application of NLR in predicting proteinuria and its severity in patients with T2DM. Therefore, further research is needed to validate these findings and determine the clinical utility of NLR in predicting proteinuria and guiding therapeutic decisions in DN.

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Conflicts of interest

There are no conflicts of interest.

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