Original Article

Relationship Between Microvascular Complications and Elevated Neutrophil-to-Lymphocyte Ratio in Patients with Diabetes Mellitus

Relación entre complicaciones microvasculares y valores elevados del índice neutrófilo-linfocito en pacientes con diabetes mellitus

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Summary

Objective: To evaluate the relationship between microvascular complications and elevated neutrophil-to-lymphocyte ratio (NLR) values in patients with type 2 diabetes mellitus (T2DM) from a family medicine unit. **Methods:** A cross-sectional analytical study was conducted at Family Medicine Unit 92 of the Mexican Institute of Social Security. A total of 232 medical records of T2DM patients were analyzed through probabilistic sampling. A data collection form, designed by the researchers, was used to collect sociodemographic, biochemical, and clinical variables, which were analyzed with GraphPad Prism 10 using χ^2 and Student's t-tests. Results with a p-value <0.05 were considered statistically significant. **Results:** NLR was calculated for each medical record, and it was found that 51 patients (22%) had elevated NLR values. Elevated NLR was associated with sex, hypertension, and poor glycemic control (p<0.05) but not with body mass index (BMI), age, and duration of T2DM. A statistically significant relationship was observed between elevated NLR and the presence of microvascular complications such as nephropathy, neuropathy, cardiopathy, and retinopathy (p<0.05). Logistic regression analysis showed a significant association between elevated NLR and diabetic cardiopathy (OR: 7.93, 95% CI, 3.29-20.33, p<0.05). **Conclusion:** Elevated NLR values were associated with the presence of microvascular complications in T2DM patients, suggesting that NLR may be useful as a biomarker for managing diabetic patients in family medicine consultations.

Keywords: Diabetic Nephropathy; Diabetic Retinopathy; Diabetic Cardiopathy; Diabetic Neuropathy; Neutrophil-to-Lymphocyte Ratio.

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Resumen

Objetivo: evaluar la relación entre las complicaciones microvasculares y valores elevados del índice neutrófilo-linfocito (NLR) en pacientes con diabetes mellitus tipo 2 (DM2) de una unidad de medicina familiar. **Métodos:** estudio transversal analítico realizado en la Unidad de Medicina Familiar 92 del Instituto Mexicano del Seguro Social. Se analizaron 232 expedientes clínicos de pacientes con DM2 obtenidos por muestreo probabilístico. Se empleó una cédula diseñada por los investigadores para la recolección de variables socio-demográficas, bioquímicas y clínicas, y se analizaron con GraphPad Prism 10 mediante pruebas de χ^2 y t de Student, los resultados con valor de $p<0.05$ se consideraron estadísticamente significativos. **Resultados:** se calculó el NLR de cada expediente y se encontró que 51 pacientes (22%) presentaron NLR elevado. La presencia del NLR elevado se relacionó con el sexo, la presencia de hipertensión y el descontrol glucémico ($p<0.05$) pero no con el índice de masa corporal, edad y tiempo de evolución de la DM2. Se encontró una relación estadísticamente significativa entre el NLR elevado y la presencia de complicaciones microvasculares como nefropatía, neuropatía, cardiopatía y retinopatía ($p<0.05$). El análisis de regresión logística mostró una relación significativa entre el NLR y la cardiopatía diabética (OR: 7.93, 95% IC, IC 3.29-20.33, $p<0.05$). **Conclusión:** Los valores elevados del NLR se relacionaron con la presencia de complicaciones microvasculares en pacientes con DM2, por lo cual el NLR puede ser empleado como un biomarcador para el control del paciente con diabetes en la consulta de medicina familiar.

Palabras clave: nefropatía diabética, cardiopatía diabética, neuropatía diabética, retinopatía diabética, índice neutrófilo-linfocito.

Introduction

Type 2 diabetes mellitus (T2DM) is the leading cause of disability, morbidity, and mortality worldwide, with an increasing global incidence. It is estimated that approximately 422 million people have the condition, the majority of whom live in low and middle income countries.[1] In Mexico, the prevalence of diabetes is 15.2%, and it is considered the second leading cause of mortality due to microvascular complications that develop over the course of the disease.[2] Among these are nephropathy, retinopathy, cardiopathy, and neuropathy, which significantly reduce both quality of life and life expectancy.[3]

Persistent hyperglycemia, advanced glycation end-products, and elevated serum lipid concentrations cause endothelial damage, resulting in a chronic inflammatory response. This condition is characterized by the production of pro-inflammatory cytokines such as TNF-alpha, IL-1B, and IL-6, which perpetuate vascular damage.[4-6] The neutrophil-to-lymphocyte ratio (NLR) has therefore been proposed as a low-cost, readily accessible inflammatory biomarker, derived from the arithmetic division of the neutrophil and lymphocyte counts in a complete blood count.[7] NLR is useful in the assessment of T2DM patients, as well as in other inflammatory, infectious, and non-infectious diseases.[8]

Forget et al.,[9] established that an NLR value >3.53 is considered elevated, and this threshold has been used in studies linking elevated NLR values to poor glycemic control in diabetes patients. Calculating NLR can complement serum glucose and glycated hemoglobin (HbA1c) measurements in screening diabetic patients.[7,10-14]

In Mexico, Maravilla et al.,[15] documented NLR as being associated with high concentrations of pro-inflammatory cytokines and a high cardiovascular risk.

In this context, the aim of this study was to evaluate the relationship between NLR and the presence of microvascular complications in T2DM patients from Family Medicine Unit No. 92 (UMF 92) of the Mexican Institute of Social Security (IMSS).

Methods

A cross-sectional analytical study was conducted from March to May 2024 at UMF 92 in Ecatepec de Morelos, Mexico, using simple random sampling. A total of 274 electronic medical records of patients diagnosed with T2DM were analyzed, of which 232 were selected based on the following criteria: patients enrolled at UMF, aged over 18 years, with at least four control visits over the past year, and with complete blood count, blood chemistry, and urinalysis reports documented in their records within the past twelve months. Forty-two records were excluded due to diagnoses of nephropathy, retinopathy, cardiopathy, and neuropathy not related to T2DM, cancer diagnoses, hematologic diseases, chronic use of anti-inflammatory drugs, and incomplete laboratory information.

A data form designed by the researchers was used to record information from the records. The form included four sections: the first section collected social security number, sex, and age; the second section recorded height, weight, body mass index (BMI), and systolic

(SBP) and diastolic blood pressure (DBP); the third section included the years since diabetes diagnosis and documented microvascular complications; the fourth section gathered biochemical parameters such as glucose, creatinine, proteinuria, HbA1c, total leukocyte, neutrophil, lymphocyte counts, NLR, and glomerular filtration rate (GFR) using the CKD-EPI 2021 formula.[16]

NLR was calculated by dividing the number of neutrophils by the number of lymphocytes and classified as normal if <3.53 and elevated if ≥3.53, according to Forget et al.,[9] BMI was calculated and categorized based on World Health Organization criteria,[17] hypertension was determined using American Heart Association (AHA) criteria,[18] and patients were classified by glycemic control according to American Diabetes Association (ADA) criteria.[19] The presence of T2DM-related microvascular complications was identified according to signs and symptoms recorded in medical notes, following established reports.[20,21] Diabetic nephropathy was documented based on a GFR value indicating KDIGO stage IIIa or higher with or without proteinuria.[22]

Descriptive statistics were performed for qualitative variables using frequency and percentage, and for quantitative variables using mean and standard deviation. Variables were evaluated by comparing two groups: patients with normal NLR and those with elevated NLR, using χ^2 test for qualitative variables and Student's t-test for quantitative variables. Values of $p<0.05$ were considered statistically significant. The data were analyzed using GraphPad Prism 10. The study was approved by local ethics and research committees and complied with IMSS regulations.

Table 1. Sociodemographic and Biochemical Variables by NLR Category

Variable		Total (%)	Normal NLR (<3.53)	Elevated NLR (≥3.53)	P value
		232 (100)	181 (78)	51 (22)	
Sex					
	Men	101 (43.5)	72 (31)	29 (12.5)	<0.05*
	Women	131 (56.5)	109 (47)	22 (9.5)	
Age (Range)					
	Young adults	28 (12.1)	23 (9.9)	5 (2.2)	0.06
	Mature adults	82 (35.3)	70 (30.2)	12 (5.2)	
	Older adults	122 (52.6)	88 (37.9)	34 (14.6)	
BMI					
	Normal weight	70 (30.2)	54 (23.3)	16 (6.9)	0.66
	Overweight	126 (54.3)	97 (41.8)	29 (12.5)	
	Obesity	36 (15.5)	30 (12.9)	6 (2.6)	
Leukocyte counts					
	Total leukocytes (Range)	7.12 ±1.44	7.03 ± 1.37	7.42 ± 1.66	<0.05*
		3.1 - 10.7	3.1-10.7	4.1-10.67	
	Total neutrophiles (Range)	4.76 ± 1.27	4.41 ± 0.97	5.97 ± 1.47	
		1.1 - 8.9	2.0-7.1	1.1-8.9	
	Total lymphocytes (Range)	2.36 ± 0.88	2.62± 0.78	1.44 ± 0.57	
		0.58 - 5.20	1.0-5.2	0.58-4.2	
Creatinine					
	Range	0.98 ± 0.87	0.84 ± 0.30	1.47 ± 1.69	<0.05*
		0.44 – 9.40	0.44 – 2.00	0.47 – 9.40	
Glomerular filtration rate					
	Range	84.73 ± 26.00	88.66 ± 26.76	70.78 ± 28.92	<0.05*
		5.00 - 140	28.00 - 140	5.00 - 121	
Serum glucose					
	Range	133.50 ± 34.58	130.00 ± 34.91	145.80 ± 30.62	<0.05*
		76.00 - 320.00	76.00 - 320.00	94.00 - 280.00	
HbA1c					
	Range	7.56 ± 0.98	7.46 ± 0.91	7.90 ± 1.13	<0.05*
		6.00-11.40	6.00 - 10.50	6.30 - 11.40	

*Statistically significant value

Results

Of the 232 records analyzed, 101 were male (43.5%) and 131 were female (56.5%), with an age range of 27 to 93 years, mean age 61.86 ± 15.16 years, most being older adults. The mean values of the results were as follows: BMI 21.99 ± 0.23 kg/m², SBP 127.6 ± 13.79 mmHg, DBP 76.03 ± 10.19 mmHg, and diabetes duration 12.22 ± 8.90 years. For biochemical variables, mean values were as follows: glucose 133.5 ± 34.58 mg/dL, HbA1c 7.56 ± 0.98%, creatinine 0.98 ± 0.87 mg/dL, GFR 84.73 ± 26.00 mL/min/1.73 m²SC, total leukocyte counts 7.12 ± 1.44 cells/mm³, neutrophil count 4.76 ± 1.27 cells/mm³, and lymphocyte count 2.36 ± 0.88 cells/mm³.

The mean NLR was 2.41 ± 1.36. Elevated NLR was identified in 51 patients (22%), of whom 29 were men (12.5%) and 22 women (9.5%). Frequency distribution for sociodemographic and biochemical variables in the groups with normal and elevated NLR is shown in Table 1.

In the search for hypertension in the records, 72 patients (31%) were identified with this condition. Additionally, diabetes control was analyzed, showing that 122 patients had controlled glucose levels (52.6%), four patients had low glucose (1.7%), and 106 patients had elevated glucose (45.7%). However, based on HbA1c levels, 149 patients had elevated HbA1c (64.2%) and 83 had controlled HbA1c (35.8%). Frequency distribution for clinical variables in the groups with normal and elevated NLR is shown in Table 2.

Based on the clinical data in the medical notes, the presence of T2DM-related microvascular complications (nephropathy, neuropathy, retinopathy, and diabetic cardiopathy) was

Table 2. Clinical Variables by NLR Category

Variable		Total (%)	Normal NLR (<3.53)	Elevated NLR (>3.53)	P value
		232 (100)	**181 (78)**	**51 (22)**	
Blood pressure					
	Normotensive	160 (69)	133 (57.3)	27 (11.6)	<0.05*
	Hypertensive	72 (31)	48 (20.7)	24 (10.4)	
Diabetes evolution time (years)					
		12.22 ± 8.90	13.94 ± 8.93	11.73 ± 8.86	
	Range	1-30	1-30	1-30	0.12
Diabetes control					
Glycemia					
	Low glucose	4 (1.7)	4 (1.7)	0 (0)	<0.05*
	Glucose in control	122 (52.6)	106 (45.7)	16 (6.9)	
	Elevated glucose	106 (45.7)	71 (30.6)	35 (15.1)	
HbA1c concentration					
	HbA1c in control	83 (35.8)	71 (30.6)	12 (5.2)	<0.05*
	Elevated HbA1c	149 (64.2)	110 (47.4)	39 (16.8)	

*Statistically significant value

Table 3. Relationship Between NLR and Microvascular Complications in Diabetic Patients from UMF 92

Variable	Total (%)	Normal NLR (<3.53)	Elevated NLR (>3.53)	P value
	232 (100)	**181 (78)**	**51 (22)**	
Diabetic nephropathy				
With diabetic nephropathy	35 (15.1)	15 (6.5)	20 (8.6)	<0.05*
Without diabetic nephropathy	197 (84.9)	166 (71.5)	31 (13.4)	
Diabetic neuropathy				
With diabetic neuropathy	53 (22.8)	31 (13.4)	22 (9.5)	<0.05*
Without diabetic neuropathy	179 (77.2)	150 (64.7)	29 (12.5)	
Diabetic retinopathy				
With diabetic retinopathy	37 (16)	17 (7.3)	20 (8.7)	<0.05*
Without diabetic retinopathy	195 (84)	164 (10.7)	31 (13.3)	
Diabetic cardiopathy				
With diabetic cardiopathy	24 (10.4)	9 (3.9)	15 (6.5)	<0.05*
Without diabetic cardiopathy	208 (89.6)	172 (74.1)	36 (15.5)	

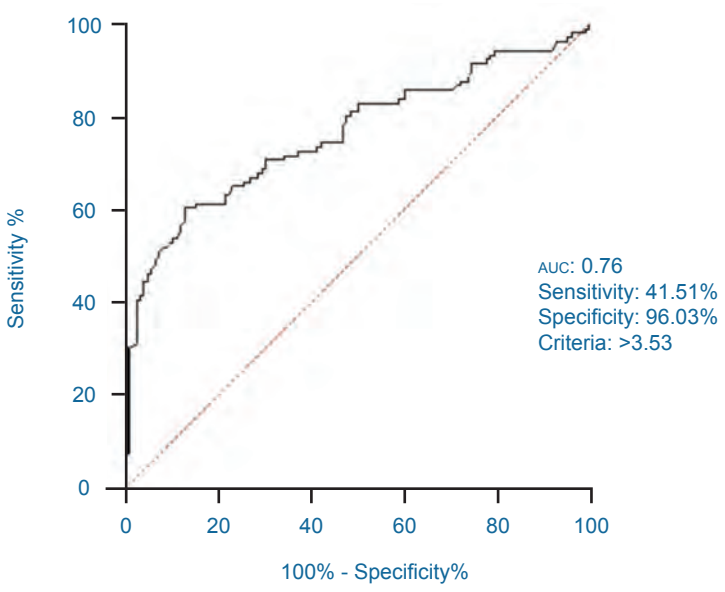
*Statistically significant value

Table 4. Multivariate Logistic Regression Analysis Between NLR and Microvascular Complications

	Regression coefficent (B)	Standard error (SE)	P value	OR	95% CI for OR	
					Lower limit	Upper limit
NLR and diabetic nephropathy	1.966	0.3936	<0.05*	7.14	3.327	15.7
NLR and diabetic neuropathy	1.3	0.3448	<0.05*	3.671	1.864	7.237
NLR and diabetic retinopathy	1.828	0.3836	<0.05*	6.224	2.948	13.37
NLR and diabetic cardiopathy	2.075	0.4597	<0.05*	7.963	3.29	20.33

*Statistically significant value

Figure 1. ROC Curve for Predicting Microvascular Complications from Type 2 Diabetes Using the NLR



AUC: Area Under the Curve

investigated, showing that 106 patients (45.7%) had at least one microvascular complication. The association between microvascular complications and NLR was statistically significant (p<0.05) (Table 3).

Multivariate logistic regression analysis estimated the relationship between microvascular complications and elevated NLR values (Table 4).

Finally, an NLR value ≥3.53 had a sensitivity of 41.51% and a specificity of 96.03%, with an AUC of 0.763 in a ROC curve (95% CI: 0.70-0.82, p<0.05).

Discussion

The development of microvascular complications due to type 2 diabetes involves pathophysiological mechanisms with an exacerbated inflammatory response, which can manifest in individuals as long-term organ damage and premature mortality.[23]

Evidence has shown a relationship between altered inflammatory biomarkers in patients with diabetes, such as C-reactive protein, interleukin-6 (IL-6), fibrinogen, adipokines, and complement proteins.[24] However, all these biomarkers have the disadvantage of being costly or having limited accessibility, which has led to the proposal of the NLR as a prognostic biomarker of mortality in patients with diabetes.[25]

In this study, we analyzed clinical records of patients with type 2 diabetes from which the NLR was obtained and categorized into two groups: those with a normal NLR and those with an elevated NLR. We found a significant association between elevated NLR and patient gender (p<0.05), being higher in men. This contrasts with findings by authors such as Mahajan et al.,[25] and Dascalu et al.,[26] who reported no relationship between NLR and patient gender. However, Majnaric et al.,[27] explain that certain factors, such as patient gender and age, influence NLR variations over time, which were not considered in any of the cited studies. This could explain the differences in the results found.

Additionally, no significant association was found between elevated NLR and patient age (p= 0.06), consistent with the findings of Chittawar et al.,[28] Meanwhile, Duman et al.,[11] reported a significant association between elevated NLR and high BMI. However, neither this study nor another report[14] found this association (p= 0.66), despite most of the studied patients being overweight (Table 1). Considering that most of the population in both studies were older adults, there may be some relationship between age and NLR values, although this point was not analyzed in detail in this study.

The simultaneous presence of diabetes and hypertension is a common finding in family medicine consultations, and NLR is also influenced by the presence of hypertension, as noted in another study.[29] In this regard, we identified a significant association between elevated NLR and hypertension (p <0.05). Likewise, the simultaneous presence of diabetes and hypertension may be associated with an increase in NLR and a higher risk of developing microvascular complications such as nephropathy and diabetic retinopathy.[30,31]

Glycemic control is a key factor in the development of microvascular complications due to type 2 diabetes, as hyperglycemia is associated with a stronger inflammatory response, evidenced by an elevated NLR.[28] Previous studies have reported an association between elevated glucose and HbA1c levels and an increase in NLR,[11,32,33] positioning NLR as a useful complementary biomarker for evaluating glycemic control in patients with diabetes, especially in situations where HbA1c is unavailable.[13,25,30,34] In this study, this statistical relationship was significant (p <0.05), associating poor glycemic control with elevated NLR values (Table 2). Our study had certain limitations. The sample size was not representative of the Mexican population, and the study was conducted using clinical record data, so the identification of microvascular complications and laboratory results were based on data recorded in medical notes and not directly through patient examination.

Although there is no universally accepted cutoff point for NLR, a value of 3.53 was used in this study, as applied in previous research. It is important to assess whether an NLR higher than 3.53 can be used as a cutoff point in the Mexican population, since, although the ROC curve estimated that NLR has potential as a predictor of microvascular complications in type 2 diabetes, the lack of standardization in the cutoff points used to calculate test sensitivity and specificity[13,25] underscores the need for additional studies to further examine this biomarker and its behavior in our population.

Conclusion

Elevated NLR values were associated with microvascular complications in T2DM patients from UMF 92, suggesting that this parameter may serve as a biomarker for managing diabetic patients in family medicine. NLR can be a complementary tool for screening and monitoring patients, enabling healthcare providers to prevent or detect microvascular complications early in the disease course.

Author contributions:

P R-C: Conceptualization, data analysis, development, results discussion, and writing; M P-P: Analysis and writing; O R-J: Analysis. All authors approve the publication of this document.

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Conflicts of Interest:

The authors declare no conflicts of interest.

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