The association between neutrophil to lymphocyte ratio and antidiabetic medications in diabetic peripheral neuropathy patients in Jeddah.

Abstract:

Introduction:

Diabetes mellitus (DM) is a major chronic systemic health concern it could develop macro- and microvascular complications. One of the commonest microvascular complications is diabetic peripheral neuropathy (DPN), Diabetic neuropathy is a type of nerve damage caused by uncontrolled hyperglycemia of diabetic patients, DPN is one of the most common causes of reduction in life quality and disability in DM patients, as well as; it overload the national health care system. Finding a cost-effective, easy prognostic marker to early detect of DPN could be an important play in prevention DM complications. Moreover, using NLR as a monitoring tool for medication that controls the hyperglycemia could have a vital role in preventing DNP. Thus, our research aims to correlate between neutrophils lymphocytes ratio (NLR) and anti-diabetic drugs in diabetic neuropathy patients with average age of 60 years.

Methodology

A retrospective, case control study was conducted on 133 patients by reviewing the data records over the period of 10 years from January 2012 to July 2022 done at king Abdul-Aziz University Hospital, Jeddah, in the western region of SA, amongst diabetic peripheral neuropathy patients who are using either oral hypoglycemic agents or insulin with regular follow ups.

Results:

The study included a total of 133 patients with most of them being male i.e., 81 (61%). The mean age of the patients is 60(SD13.5) years. Approximately two-third of the patients 86(64.7%) had diabetic for more than 10 years. There was no significant association identified for gender, age group, nationality, and medication ($p > 0.05$) with HbA1c or NLR. Moreover, that there was no significant association between NLR and HbA1c categories.

Conclusion:

In conclusion our study showed non-significant relationship between NLR and DPN among elderly diabetic patient at King Abdu al-aziz university hospital (KAUH).

Kye words:
Type 2 diabetes, Antidiabetic medications, neutrophil to lymphocyte ratio (NLR), peripheral neuropathy.

Introduction:

Diabetes mellitus (DM) is a major chronic systemic health concern in 2015[1]. The Diabetes Federation estimated that 415 million adults were diagnosed with Diabetes, and they predicted that by 2040 one in ten adults would develop diabetes [2]. Throughout the past two decades, multiple studies in Saudi Arabia were Conducted and showed that the prevalence of diabetic patients significantly increased[3]. The most recent survey showed that the prevalence of DM in Jeddah was 18.3% based on World Population[4]. The principle of diabetes management includes being active, a healthy diet and Medications. FDA has approved many classes of oral antidiabetic medications, Injectable agents, and insulin products to treat type 2 diabetes [1]. Oral Antidiabetic medications include sulfonylureas, biguanides, α-glucosidase inhibitors, Thiazolidinediones, and sodium-glucose cotransporter 2 Inhibitors. Among them, Metformin remains the first option for treating most type 2 DM patients[5]. DM could develop macro- and microvascular complications[6]. One of the commonest microvascular complications is diabetic peripheral neuropathy (DPN)[7]. Diabetic neuropathy is a type of nerve damage caused by uncontrolled hyperglycemia of diabetic patients[8]. Many studies have been showed that DPN is not developed only because of Microvascular complications of DM[9]; moreover, inflammation plays a crucial role in progressing DPN [10]. Therefore, a growing body of literature has investigated the using of neutrophil Lymphocyte ratio (NLR) as a prediction marker for DPN. NLR has been used to predict the prognosis of other diseases such as end-stage renal failure[11], Atherosclerosis[12], and cancer[13]. NLR is used for Screening diseases and drug monitoring tool. It is preferable over other inflammatory Markers because of its wide availability, low cost, reliability, easy lab detection [14]. The relationship between DPN and NLR were observed in several studies, but none focused on elderly patient and the effect of anti-diabetic drugs on using NLR as a prognostic marker for DPN in DM patients. The purpose of this retrospective study is to compare the neutrophil-to-lymphocyte ratio (NLR) in diabetic peripheral neuropathy (DPN) patients who are their average age 60 years, and on different classes of antidiabetic drugs (e.g., insulin, metformin, and sulfonylurea combination)

Methodology:

Study design and setting

A retrospective, case control study was conducted by reviewing the data records over the period of 10 years from January 2019 to December 2021 done at king Abdul-Aziz University Hospital, Jeddah, in the western region of SA, amongst diabetic peripheral neuropathy patients who are using either oral hypoglycemic agents or insulin with regular follow ups.

All diabetic patients younger than 18 years old and gestational diabetes, those who have a history of malignancy, autoimmune disease, hematological disorder, other DM complications and patients diagnosed with infectious diseases at the time of collecting lab results. In addition to patients on

immunosuppressant's or corticosteroids with single visit or incomplete follow up were excluded from the study.

Sample size and sampling procedure

The sample size was calculated for this study is 133 patients with 95% confidence level and 5%, a margin of error. The calculations were made using the Rao soft sample size calculator [15].

Data collection instruments

The data was collected via the electronic documentation system used at KAUH (**phoenix system**), and it was categorized into five sections. To begin with section one, was about the demographic data which include age, gender, nationality. Section two is consisted of Medications started with Insulin, OHG or both. Section three is composed of HbA1c which divided into excellent and poor. Section four was containing the duration of DM (≤5 years, 6-10 years and >10 years). In conclusion with section five is allocated to determine the NLR (Low/Medium or High)**.**

Analysis

Microsoft Excel version 2016 was used for data entry. Regarding data analysis, data were coded, checked, and entered into the Statistical Package for the Social Sciences (IBM® SPSS®, Armonk, NY) version 26.
The categorical variables, consisting of demographic information were expressed as frequencies and percentages, and measures of central tendency were calculated for the continuous variables, including means ± standard deviations, range, median and dispersion. Chi-squared test was used to compare between varies variables with a p-value <0.05 to indicate statistically significant.

Research ethics

Access to data was available only to the principal investigator to ensure the privacy and confidentiality of participants.

Results:

The study included a total of 133 patients with the majority of them being male i.e., 81 (61%). The mean age of the patients is 60 (SD13.5) years. The median value for NLR and HbA1c is 2.8(IQR18.86-5.06) and 8.9(IQR7.14-10.60) respectively. The median duration for being diabetic is 15(IQR10-24.5) years. More than half 73(54.9%) were non-Saudi and almost all the patients (98.5%) were older than 30 years as shown in Table 1. There were 13 (9.8%) patients who were taking both

Insulin and oral hypoglycemic, and another 74 (55.6%) were taking Insulin alone. The HbA1c was excellent in 29 (21.8%), poor in 104(78.2%) of the patients. Approximately two-third of the patients 86(64.7%) had diabetic for more than 10 years as well as Neutrophil-Lymphocyte Ratio.

Table 2 compares the association between the demographic variables and duration of diabetes with the HbA1c categories. There was no significant association identified for gender, age group, nationality, and medication (p >0.05). The duration of diabetes mellitus was found to be associated with the HbA1c categories with 86% of patients having duration of diabetes more than 10 years being in the poor category as compared to 50% in those having diabetes for ≤5 years (p=0002).

Table 3 shows the comparison of the demographic variables with Neutrophil-Lymphocyte Ratio. There was no significant association found between any of the demographic variables and duration of diabetes with NLR (p>0.05).

Table 4 shows that there was also no significant association between NLR and HbA1c categories. Figure 1 shows the scatter plot between NLR and HbA1c and it was found that there is weak positive correlation with no significant correlation between the two $r_s=0.073$, $p=0.402$, $N=133$.

Table 1: The sociodemographic and medical characteristics of the study population

	Mean	**SD***
Age	60.01	13.52
	Median	**IQR**
Duration Of DM** (Y)	15.0	10-24.5
NLR^	2.8	1.87-5.05
Hb1AC	8.9	7.14-10.6
	N	**%**
Gender		
Male	81	60.9
Female	52	39.1
Nationality		
Saudi	60	45.1
Non-Saudi	73	54.9

Medication		
Insulin	74	55.6
OHGɨ	46	34.6
Both	13	9.8
Age		
18-30 years	2	1.5
>30 years	131	98.5
HbA1c		
Excellent	29	21.8
Poor	104	78.2
Duration		
≤5 Years	18	13.5
6-10 Years	29	21.8
>10 Years	86	64.7
NLR		
Low/medium	47	35.3
High	86	64.7

**DM: Diabetes mellitus, *SD: Standard deviation

^NLR: Neutrophils lymphocytes ratio, ɨOHG: Oral hypoglycemic agents

Table 2: Comparative statistics of HgA1c between the subgroups of the study population

	HgA1c				
	Excellent (n=29)		**Poor (n=104)**		**P-value**
	N	**%**	**N**	**%**	
Gender					
Male	19	23.5%	62	76.5%	0.565*
Female	10	19.2%	42	80.8%	
Age					
18-30 years	1	50.0%	1	50.0%	0.390**
>30 years	28	21.4%	103	78.6%	
Nationality					
Saudi	11	18.3%	49	81.7%	0.379*
Non-Saudi	18	24.7%	55	75.3%	
Duration					
≤5 years	9	50.0%	9	50.0%	0.002*
6-10 years	8	27.6%	21	72.4%	
>10 years	12	14.0%	74	86.0%	
Medication					
Insulin	16	21.6%	58	78.4%	0.804*
OHG^	11	23.9%	35	76.1%	
Both	2	15.4%	11	84.6%	

	n	Mean Rank	Mann-Whitney U	Z	P-value
NLR#			1355	-0.834	
Excellent	29	72.28			0.404ɨ
Poor	104	65.53			

^OHG: Oral Hypoglycemic agents, #NLR: Neutrophils lymphocytes ratio, *Chi-square test

**Fisher exact test, ɨMann-Whitney U test

Table 3: Comparative statistics of neutrophils lymphocytes ratio between the subgroups of the study population

	NLR^				
	Low/Medium(n=47)		High(n=86)		p
	n	%	n	%	
Gender					
Male	25	30.9%	56	69.1%	**0.178***
Female	22	42.3%	30	57.7%	
Age					
18-30 years	0	0.0%	2	100.0%	**0.540****
>30 years	47	35.9%	84	64.1%	
Nationality					
Saudi	22	36.7%	38	63.3%	**0.771***
Non-Saudi	25	34.2%	48	65.8%	
Duration					
=<5 years	9	50.0%	9	50.0%	
6-10 years	10	34.5%	19	65.5%	**0.369***
>10 years	28	32.6%	58	67.4%	
Medication					
Insulin	29	39.2%	45	60.8%	
OHG#	13	28.3%	33	71.7%	**0.462***
Both	5	38.5%	8	61.5%	
	n	**Mean Rank**	**Mann-Whitney U**	**Z**	**p**
Gender					
Male	81	71.93	1707	1.840	**0.066ɪ**
Female	52	59.33			
Nationality					
Saudi	60	64.43	2036	0.696	**0.486ɪ**
Non-Saudi	73	69.11			
Age					
18-30 years	2	65.50	128	0.055	**0.956ɪ**
>30 years	131	67.02			
	n	**Mean Rank**	**Chi-Square**	**df**	**p**
Duration					
=<5 years	18	58.44			
6-10 years	29	65.00	1.317	2	**0.518ʜ**
>10 years	86	69.47			
Medication					
Insulin	74	65.54	0.591	2	**0.744ʜ**
OHG	46	70.41			

Both	13	63.23

^NLR: Neutrophils lymphocytes ratio, #OHG: Oral Hypoglycemic agents, *Chi-square test **Fisher exact test, ɨMann-Whitney U test, ɨɨKrustal Wallis test

Table 4: Association of Hga1C and neutrophils lymphocytes ratio

	NLRɨ					
	Low/medium		High			P-Value
	N=47 %		N=86 %		OR	95% CI	
HgA1c							
Excellent	8	27.6%	21	72.4%	0.635	0.257-1.571	0.323*
Poor	39	37.5%	65	62.5%			

ɨ*NLR:* Neutrophils lymphocytes ratio, **Chi-square test*

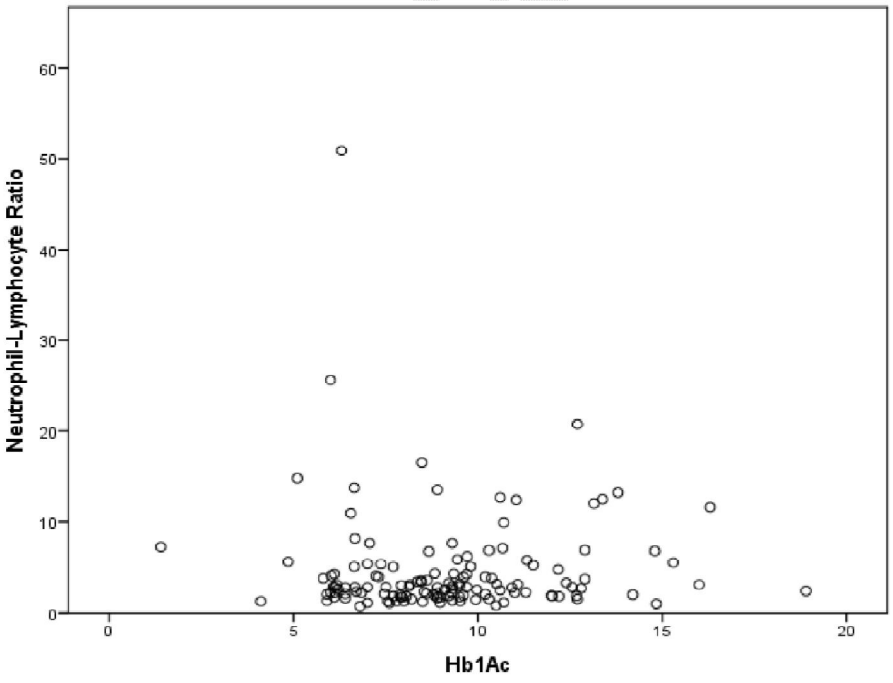

Figure 1: Scatter plot showing a week positive correlation between Neutrophils lymphocytes ratio and HbA1c.

Discussion:

DPN is a microvascular complication of T2DM which is caused by chronic inflammatory proses and dysfunction of immune system. Therefore, several studies have been done to assist the best and easiest marker for early detection of microvascular complication specially DPN. Results have demonstrated that there are many inflammatory mediators associated with developing DPN, Like NLR, platelet-lymphocytic ratio (PLR) and lymphocyte-monocyte ratio (LMR) [16].

Regarding NLR, it is a traditional marker which has various advantages over other inflammatory markers because of its wide availability, low cost, reliability, easy lab detection. Moreover, NLR can be used as population screening, disease and drug monitoring tool on large scale basis. Even patients with increase NLR but normal TLC count could have increased risk of atherosclerosis related diseases.[13,17,18] Most of the past studies have showed a significant relationship between high levels of NLR and neurovascular complication, such as cardiomyopathies, retinopathies, chronic kidney disease and DPN [1,17,19,20]. But no specific studies focused on its role in elderly patient. Therefore, in the present study we aim to correlate between neutrophils lymphocytes ratio (NLR) and anti-diabetic drugs in elderly patients.

In this study the average age is 60 years with sample size of 133 patients. More than half 73(54.9%) were non-Saudi and approximately two-third of the patients 86(64.7%) had diabetic for more than 10 years. There was no significant association identified for gender, age group, nationality, and medication ($p > 0.05$). Also, there was no significant association found between any of the demographic variables and duration of diabetes with NLR ($p > 0.05$). Moreover, there was no significant association between NLR and HbA1c categories.

Unexpectedly, our results were opposite to past studies that showed significant relationship between high NLR and DPN in T2DM [21] or other long-term diabetes related complications[15,20]. Even though NLR has lots of advantages, it can be affected by some common physical conditions, such as dehydration Furthermore, physical exercise and release of catecholamine (CA) can cause a drop in neutrophilic granulocyte and lymphocyte[22]. So, In addition to NLR there are other inflammatory markers that can be used for early detection and assisting the severity of neurovascular complications in T2DM. For example, research conducted in Turkey, Erzincan University found that PLR is a good predictive marker for chronic inflammation in diabetic patient[23]. Poorly controlled diabetes mellitus, as reflected by elevated HbA1c values and disease complications, is associated with a small but statistically significant elevation of ANC and ALC values[24]. High levels of HbA1C and diabetic complications reflecting a poor control statues of diabetes mellitus, is related with significant elevation of absolute neutrophil counts (ANC) and absolute lymphocyte counts (ALC) according to a study done in Kuwait[24].

Our study has focused on the relationship between NLR, and the types of anti-diabetic drugs used among patients with an average age of 60 years old, the specificity of the study objective provides a point of strength that can add to the literature and help physicians put in consideration the utility of NLR results in correlation with types of drugs. However, the nature of retrospective design relies on the hospital record system which may lack some information regarding the latest laboratory results and loss of follow-up for some patients. Moreover, conducting the study in a single center has

resulted in a small sample size which may reduce the power to reveal the true association between NLR and types of anti-diabetic drugs.

Conclusion

The present study investigated the differences in neutrophils lymphocytes ratio among patients suffering from diabetic neuropathy in relationship to different anti-diabetic drugs. The results showed no statistically significant differences between the classes of drugs in the results of neutrophils lymphocytes ratio at King Abdu al-Aziz university hospital, Jeddah, Saudi Arabia. While not statistically significant, the NLR had a weak positive correlation with the results of HgA1c. We recommend conducting multi-center studies with larger sample size to investigate the true effect of drugs on the NLR among patients with diabetic neuropathy.

Ethical approval:
The study was approved by the Medical Ethics Committee of King Abdul-Aziz University in December 2919 (Ethical approval reference No 652-19).

Data and material availability:
All data associated with this study are present in the paper.

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