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Neutrophil Lymphocyte Ratio as a Tool in Predicting Glycemic Control in Type 2 Diabetic Mellitus

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ABSTRACT
In recent times, NLR emerged as a novel and reliable indicator of underlying systemic inflammatory response in various diseases. NLR can be a reliable biomarker of ongoing low grade inflammation in various medical conditions such as metabolic syndrome, Hypertension and Diabetes Mellitus. To study Neutrophil Lymphocyte Ratio as a tool in predicting glycemic control in Type 2 Diabetes Mellitus. A cross sectional study was conducted on 100 adult patients confirmed with Type 2 Diabetes mellitus attending Department of General Medicine, Government General Hospital, Kadapa. In diabetic patients, NLR deterioration is associated with poor glycemic control, which increases the importance of hemogram in diabetic patients. In cases in which HbA1c measurement cannot be performed and if the glycemic condition is not evaluated earlier, NLR can be a useful examination. Improvement of NLR after glycemic regulation has suggested that this parameter may be useful in monitoring treatment response. NLR may be useful as an easily measurable, noninvasive, available and cost-effective parameter for the monitoring glycemic control and treatment response in diabetic patients.

INTRODUCTION

Diabetes Mellitus (DM) is a highly prevalent metabolic disorder that alters the blood glucose levels. Low grade inflammation has a vital role in pathogenesis of Type 2 DM, leading to development of insulin resistance. Chronic inflammation plays a vital role in the development of micro vascular and macro vascular complications[1]. The HbA1c in blood measures the average blood glucose levels over three months and helps in disease management. Higher HbA1c levels indicate poorer outcomes. HbA1c is one of the most often utilized tests to monitor management of Type1 and Type 2 DM[2]. But HbA1c is unable to identify the underlying inflammatory changes. The neutrophil lymphocyte ratio (NLR) can easily identify and monitor such conditions[3]. In recent times, NLR emerged as a novel and reliable indicator of underlying systemic inflammatory response in various diseases. NLR can be a reliable biomarker of ongoing low grade inflammation in various medical conditions such as metabolic syndrome, Hypertension and Diabetes Mellitus[4]. Elevated NLR has been reported in multiple other inflammatory diseases including inflammatory bowel disease and Covid 19 infection[5,6]. In various clinical settings, NLR has been found to be an independent predictor of major mortality, morbidity and long term survival[7]. It can also be used as a tool for screening of population, detection of disease and monitoring drug therapy. Neutrophils are the major leukocytes in blood stream that respond rapidly to ongoing inflammatory stimuli leading to increased neutrophil levels in the blood. Inflammatory stimuli can also cause increase in interleukin levels which in turn causes neutrophilia and lymphopenia, hence can be used together as a ratio called Neutrophil Lymphocyte Ratio (NLR). A high neutrophil value is a marker of the ongoing, non specific inflammatory process. Conversely, a low lymphocyte count indicates immune dysfunction and also a quiescent immune regulation. Hence, higher NLR levels can indicate the functional status of the immune system in the course of chronic inflammation. NLR is also relatively stable compared to other individual white blood cell investigations[8]. NLR is widely available, low cost parameter that has been and can be investigated as a more reliable proxy marker of systemic chronic inflammation. Recently, multiple studies have proved association and correlation between NLR and DM and thus this has been a current issue of investigation.

Aims: To study Neutrophil Lymphocyte Ratio as a tool in predicting glycemic control in Type 2 Diabetes Mellitus.

Objectives: To correlate Neutrophil Lymphocyte Ratio with HbA1c (standard predictor of glycemic control), fasting blood sugar (FBS), postprandial blood sugar (PPBS)., with risk factor of diabetes (lipid profile, age) and complications of type 2 diabetes mellitus (Diabetic nephropathy)., with risk factors like age, lipid profile.

MATERIALS AND METHODS

A cross sectional study was conducted on 100 adult patients confirmed with Type 2 Diabetes mellitus attending Department of General Medicine, Government General Hospital, Kadapa. Correlation of Neutrophil Lymphocyte ratio with age, lipid profile, BMI, duration of diabetes, HbA1C, FBS, PPBS, Proteinuria was done.

RESULTS AND DISCUSSIONS

In our study 51% of the patients were females followed by males were 49%. Majority of our patients were having history of diabetes for 6-10 years i.e., 49% of the patients. Duration of Diabetes was 2-5 years in 31%, 11-15 years in 16% and 1 year in 1% of Patients. Mean duration of diabetes was 6.94±3.36 years. In our study 41% of the patients had the history of Hypertension along with diabetes.

Table 1: Age wise Distribution of the Patients

Age group	Number	Percentage
31-40 years	16	16
41-50 years	27	27
51-60 years	34	34
>60 years	23	23
Mean±SD	52.4±10.4 years	

Table 2: Distribution Depending on BMI

BMI	Number	Percentage
Normal	31	31
Overweight	41	41
Obese	28	28
Total	100	100
Mean±SD	27.9±4.56 Kg/m2	

Table 3: FBS Levels in the Study Patients

FBS Groups	Number	Percentage
<100 mg/dl	12	12
101-120 mg/dl	15	15
121-140 mg/dl	13	13
>140 mg/dl	60	60
Mean±SD	146±33.7 mg/dl	

Table 4: PPBS Levels in the Study Patients

PPBS Groups	Number	Percentage
<150 mg/dl	14	14
151-200 mg/dl	28	28
201-250 mg/dl	29	29
251-300 mg/dl	14	14
>300 mg/dl	15	15
Mean±SD	222±65.2 mg/dl	

Table 5: Triglycerides in the Study Patients

Triglycerides	Number	Percentage
<150 mg/dl	13	13
151-200 mg/dl	46	46
201-250 mg/dl	24	24
>250 mg/dl	17	17
Mean±SD	204±49.3 mg/dl	

Table 6: HDL levels in the Study Patients

HDL values	Number	Percentage
21-30mg/dl	33	33
31-40mg/dl	37	37
>40mg/dl	30	30
Total	100	100
Mean±SD	34.8±7.21mg/dl	

Table 7: Categorization of the Patients Depending on HbA1C

HbA1C	Number	Percentage
≤7	32	32
>7	68	68
Total	100	100

Table 8: Association of Age Group with NLR

Age group	NLR <2	NLR >2	Total
31-40 years	8(18.6)	8(14)	16
41-50 years	8(18.6)	19(33.3)	27
51-60 years	16(37.2)	18(31.6)	34
>60 years	11(25.6)	12(21.1)	23
Total	43	57	100
Chi square test :2.74, df: 3, P=0.434 Not significant			
Mean±SD	53.12±10.37	51.84±10.13	52.4±10.4
Students t test: 0.616, df : 98, p=0.539., Not significant			

Table 9: Association Between Gender and NLR

Gender	NLR <2	NLR >2	Total
Male	19(44.2)	30(52.6)	49
Female	24(55.8)	27(47.4)	51
Total	43	57	100
Chi square test: 0.7, df: 1, P=0.403., Not significant			

Table 10: Association Between BMI and NLR

BMI	NLR <2	NLR >2	Total
Normal	9(20.9)	22(38.6)	31
Overweight	16(37.2)	25(43.9)	41
Obese	18(41.9)	10(17.5)	28
Total	43	57	100
Chi square test :7.91, df: 2, P=0.019 Significant			
Mean±SD	29.43±4.84	26.74±3.96	27.9±4.56
Students t test: 3.063, df: 98, p 0.003., Significant			

Table 11: Association Between Duration of Diabetes and NLR

Duration of diabetes	NLR <2	NLR >2	Total
≤1 year	2(4.7)	2(3.5)	4
2-5 years	12(27.9)	19(33.3)	31
6-10 years	19(44.2)	30(52.6)	49
11-15 years	10(23.3)	6(10.5)	16
Chi square test :3.15, df: 3, P 0.369, Not Significant			
Mean±SD	7.53±3.45	6.09±3.27	7.01±3.36
Students t test: 2.139, df: 98, P=0.035., Significant			

Table 12: Association of History of Hypertension and NLR

HTN		NLR <2	NLR ≥2	Total
Absent	Observed	23	36	59
	% within column	53.5%	63.2%	59.0%
Present	Observed	20	21	41
	% within column	46.5%	36.8%	41.0%
Total	Observed	43	57	100
	% within column	100.0%	100.0%	100.0%
Chi square test : 0.947, df: 1, P 0.33 Not Significant				

Table 13: Association Between FBS and NLR

FBS	NLR <2	NLR >2	Total
<100 mg/dl	07(16.3)	05(8.8)	12
101-120 mg/dl	09(20.9)	06(10.5)	15
121-140 mg/dl	09(20.9)	04(7)	13
>140 mg/dl	18(41.9)	42(73.7)	60
Chi square test : 10.7, df: 3, P 0.013 Significant			
Mean±SD	133.42±26.7	154.79±35.7	146±33.7
Students t test: -3.29, df: 98, p 0.001 Significant			

Table 14: Association Between PPBS and NLR

PPBS	NLR <2	NLR >2	Total
<150 mg/dl	10(23.3)	4(7)	14
151-200 mg/dl	15(34.9)	13(22.8)	28
201-250 mg/dl	16(37.2)	13(22.8)	29
251-300 mg/dl	1(2.3)	13(22.8)	14
>300 mg/dl	1(2.3	14(24.6)	15
Chi square test : 23.1, df: 4, P<0.001 Significant			
Mean±SD	187.8±44.78	247±66.87	222±65.2
Students t test: -5.02, df: 98, p<0.001 Significant			

Table 15: Association Between HbA1C with NLR

	Glycemic control	NLR <2	NLR >2	Total
Poor	Observed	20	48	68
	% within column	46.5%	84.2%	68.0%
Good	Observed	23	9	32
	% within column	53.5%	15.8%	32.0%
Total	Observed	43	57	100
	% within column	100.0%	100.0%	100.0%
Chi-square test =16, df : 1, p value : <0.001				
	Mean±SD	7.36±1.51	10.85±3.25	9.35±3.16
Students t test: -6.52, df: 98, P=<0.001 Significant				

Table 16: Association Between Triglycerides and NLR

Triglycerides		NLR <2	NLR ≥2	Total
< 150 mg/dl	Observed	7	6	13
	% within column	16.3%	10.5%	13.0%
151-200mg/dl	Observed	19	27	46
	% within column	44.2%	47.4%	46.0%
201-250mg/dl	Observed	11	13	24
	% within column	25.6%	22.8%	24.0%
>250mg/dl	Observed	6	11	17
	% within column	14.0%	19.3%	17.0%
Total	Observed	43	57	100
	% within column	100.0%	100.0%	100.0%
Chi square test : 1.17 , df : 3, p value : 0.761, Not Significant.				
Mean±SD	198.56±47.45	209.77±50.55		204±49.3
Students t test: -1.027, df: 98, P0.307 Not Significant				

Table 17: Association Between Categories of HDL and NLR

HDL		NLR <2	NLR ≥2	Total
<40 mg/dl	Observed	33	37	70
	% within column	76.7%	64.9%	70.0%
>40 mg/dl	Observed	10	20	30
	% within column	23.3%	35.1%	30.0%
Total	Observed	43	57	100
	% within column	100.0%	100.0%	100.0%
Chi square : 1.63 , df : 1, p value : 0.201 , Not significant				
	Mean±SD	33.79±6.66	35.47±7.58	34.8±7.21
Students t test: -1.158, df: 98, P=0.25 Not Significant				

Table 18: Association Between NLR and Proteinuria (Complication of Diabetes)

Proteinuria		NLR <2	NLR ≥2	Total
Absent	Observed	31	23	54
	% within column	72.1%	40.4%	54.0%
Present	Observed	12	34	46
	% within column	27.9%	59.6%	46.0%
Total	Observed	43	57	100
	% within column	100.0%	100.0%	100.0%
Chi square test χ^2	9.94	df :1	P=0.002 Significant	

Table 19: Correlation of NLR with Lipid Profile, HbA1c and Proteinuria

		NLR	Proteinuria	Duration of Diabetes	FBS	PPBS	HbA1C	TAG
Proteinuria								
	Pearson's r	0.356	—					
	P	0.002	—					
Duration of Diabetes	Pearson's r	-0.19	0.02	—				
	p-value	0.035	0.845	—				
FBS	Pearson's r	0.307	0.003	-0.056	—			
	p-value	0.001	0.975	0.581	—			
PPBS	Pearson's r	0.451	-0.092	-0.149	0.361	—		
	p-value	< 0.001	0.364	0.139	< .001	—		
HbA1C	Pearson's r	0.529	-0.122	-0.141	0.651	0.696	—	
	p-value	< 0.001	0.225	0.16	< .001	< .001	—	
TG	Pearson's r	-0.13	-0.245	-0.167	0.061	0.034	-0.028	—
	p-value	0.307	0.014	0.097	0.549	0.735	0.782	—
HDL	Pearson's r	0.082	0.085	0.093	0.173	-0.07	0.044	0.018
	p-value	0.25	0.399	0.356	0.084	0.513	0.664	0.86

Table 20: NLR as Diagnostic Tool to Predict the Glycemic Control

		95% Confidence Interval	
	Ratios	Lower	Upper
Sensitivity	70.6%	58.3%	81.0%
Specificity	71.9%	53.3%	86.3%
Accuracy	71.0%	61.1%	79.6%
Prevalence	68.0%	57.9%	77.0%
Positive Predictive Value	84.2%	72.1%	92.5%
Negative Predictive Value	53.5%	37.7%	68.8%
Posttest Disease Probability	84.2%		
Posttest Health Probability	53.5%		
Positive Likelihood Ratio	2.51		
Negative Likelihood Ratio	0.409		

According to Li[9] a study of NLR done in healthy population based on different age groups showed that NLR increases with age. In the age group of ≥70 years, mean NLR was reported to be highest with a value of 1.99 and SD of 0.6. Also, NLR statistically correlated with age. Thus an arbitrary cut off of 2 was taken for NLR in our study. Majority of our study population comprised of 51-60 years age group i.e., 34%. Mean

age of the study population was 52.4±10.4 years. Our patients aged from 32 years to 69 years. Similar results were seen in the study by Gurmu[10] where the mean age among patients with and without diabetic nephropathy was compared. Diabetics with nephropathy had mean age of 60.36±10.30 compared to diabetics without nephropathy with a mean age 53.85±11.90. In the similar study done by Akin[18] the median age of the study group was calculated to be 49 (45-51) years similar to our study with a mean age of 52.4±10.4 years. In a study done by Duman[11] positive correlation of NLR was seen with age (r=0.26 p=0.008) in contrast to our study. In current study, 51% of the patients were female followed by 49% were males. It was observed that, mostly females were observed to have NLR <2 (55.8%, n=24/43) and males were mostly having NLR ≥2 (52.6%, n=30/57) (p=0.403). In the study by Gurmu[17] and Akin[12] females were more among the study groups (62.2% and 64.7%) similar to our study. In study done by Kahraman[13] no statistical significance was found between gender and NLR. Duration of diabetes was 2-5 years in 31% of patients, 11-15 years in 16%, ≤1 year in 4% of patients. Mean duration of diabetes in our study was 6.94±3.36 years. In the study by Gurmu *et al,* highly significant differences were observed among the two groups regarding duration of diabetes. 43 patients had NLR <2 and 57 patients had NLR ≥2. Mean BMI among patients with NLR <2 was 29.43±4.84, while in patients with NLR ≥2, was 26.74±3.96 kg/m2. This difference was statistically significant at p<0.05 with NLR <2 group having higher mean BMI than the other group. In current study, total, 41 patients had the history of hypertension along with diabetes. No statistical significance is seen in relation to hypertension in both the groups. In a study done by Akin *et al,* 45.9% patients had hypertension. Statistical correlation with NLR was not seen in this study similar to our study. Mean FBS levels among patients with NLR ≥2 was 154.79±35.7mg/dl. In a similar study done by Akin *et al,* where diabetics, classified into poor and good glycemic control groups, were compared with healthy controls, FBS levels were higher in poor glycemic group with a median of 225 mg/dl. In our study, patients with NLR ≥2 had high FBS levels compared to patients with NLR <2 which was proven to be statistically significant. In similar study done by Chen[14] in diabetic patients secondary to exocrine pancreatic disorders, NLR values were significantly associated with FBS levels (p value<0.001) and NLR was found to be an independent risk factor for diabetes secondary to exocrine pancreatic disorders. In Duman[11] where diabetics were compared to healthy controls, median NLR was significantly higher in diabetic group (1.9 vs 1.5) and NLR strongly correlated to FBS levels (r=0.35, p=<0.001). In Shiny[15] subjects with DM had higher NLR levels (2.2±1.12) and NLR showed significant positive correlation to FBS levels (r=0.378, p<0.001). NLR showed linear increase with increasing severity of glucose intolerance. Mean PPBS levels among patients with NLR ≥2 was 247±66.87mg/dl compared to NLR <2 group with mean PPBS of 187.8±44.78 mg/dl. On statistical analysis, patients with NLR ≥2 had high PPBS levels compared to patients with NLR <2 which was proven to be statistically significant (p<0.001). Gradual increase in PPBS values was seen in patients with NLR ≥2. These PPBS when correlated with FBS proved to be statistically significant with a P value of <0.001 thus suggesting that patients with higher FBS levels are prone to have higher PPBS levels and thus tend to have higher NLR values. Mean Triglycerides levels in our study population was 204±49.3 mg/dl. Triglyceride levels in our study population ranged from 108-303 mg/dl. In the similar study done by Akin *et al,* 42.4% had hyperlipidemia. No statistical analysis was done for TG with NLR values in this study. In a study done by Lou[16] where diabetic patients grouped into insulin resistance (IR) group and no insulin resistance group, were compared with healthy controls, TG levels were higher in IR group compared to other two groups. Mean HDL levels in our study was 34.8±7.21 mg/dl. Majority of the patients with NLR ≥2 had HDL levels <40 mg/dl. Similar study done by Lou *et al,* showed lower HDL levels in diabetic patients with IR. No statistical association was seen with HDL and IR in this study. IR was not independently correlated to HDL. In our study, NLR did not show statistical association with HDL levels. In our current study, subjects were classified into good glycemic control group with HbA1c ≤7% and poor glycemic control group with HbA1c >7%. Majority of the patients in our study have poor glycemic control (68% cases). Mean HbA1C levels among patients with NLR ≥2 was 10.85±3.25 and with NLR <2 was 7.36±1.51. There is a significant statistical correlation of HbA1c with NLR in our study with a significant p value of <0.001 suggesting patients with NLR ≥2 had higher HbA1c levels. Sefil[17] studied diabetic patients classified into two groups with HbA1c ≤7% and HbA1c >7% and found that NLR had a positive correlation with HbA1c (r=0.577., p<0.001). In a study by Duman[11] Median NLR was higher in type2 DM compared to healthy controls (2.44 vs 1.5) and NLR strongly correlated with HbA1c with a statistical r value of 0.51 and p value of <0.001. Shiny et al studied Asian Indians with normal glucose tolerance, impaired glucose tolerance, type 2 DM and found higher NLR values in type 2 DM group compared to other two groups. There was a positive correlation of NLR with HbA1c with a significant r value of 0.411. Also a linear increase in NLR was seen with increasing severity of glucose tolerance. Among patients with NLR ≥2, majority of the patients had proteinuria (59.6%). On statistical analysis, difference in proteinuria was statistically significant among the two groups (p=0.002)

proving that NLR will be higher in diabetic patients with proteinuria. In a study done by Li X *et al,* where NLR was correlated with Diabetic Kidney Disease (DKD) in diabetic patients, positive correlation and association was seen between NLR and DKD prevalence. According to this study, NLR can also serve as a potential inflammatory marker for identifying risk of DKD. In a study done by D and M[18] which was done in uncontrolled diabetic patients (HbA1c >10%), 33% patients were proteinuric and NLR values were higher in proteinuric patients. In the study by S[19] NLR had a positive correlation with urinary ACR levels. NLR values were higher in patients with proteinuria. Assulyn[20] studied type 2 DM patients with parameters such as microalbuminuria and NLR. This study found that NLR has an association (p value=0.003, r=0.214) and Positive Predictive Value for microalbuminuria in diabetic patients. A study by R[21] evaluated association of NLR with early renal dysfunction and albuminuria and found that NLR was positively correlated to Urinary albumin excretion. In the study done by Mc[22] higher baseline NLR levels were seen in patients with proteinuria and NLR independently predicted significant progressive renal impairment and albuminuria progression in Type 2 Diabetes Mellitus patients. In the study by Li[23] NLR was associated with albuminuria (p value=0.0224). Baris Afsar studied albuminuria and 24hr urinary protein in newly diagnosed type 2 DM patients and found an independent relation between NLR and albuminuria. In Hussain *et al,* NLR was found to be an independent marker of worst diabetes. In Chen[14] NLR is an independent risk factor for diabetes for exocrine pancreatic disorders. According to Guo[24] NLR was associated with the incidence and prevalence of T2DM. This result suggests that the NLR is a predictor for the development of diabetes. In Lee[25] NLR was an independent risk factor for long term complications in diabetic patients. In Ozturk[26] a significant relation of NLR was found with retinopathy. In geriatric patients, there was an increased prevalence of microvascular complications with increasing NLR. Xu[27] showed that NLR is significantly correlated with diabetic polyneuropathy, which suggested that NLR may be an independent risk factor of diabetic neuropathy. In our study, NLR was strongly and positively correlated with Fasting blood glucose, Post prandial blood glucose, HbA1c, complication of diabetes (proteinuria). NLR was not associated with lipid profile, age and gender. Based on these statistical correlations, NLR can be used as an indirect marker of high fasting and postprandial glucose levels and also correlates with increased risk of renal impairment (proteinuria) especially in long standing uncontrolled diabetes. Since HbA1c is an expensive marker of uncontrolled diabetes, NLR being a cheap, inexpensive marker can be used to predict higher glucose levels in diabetics prior to testing HbA1c in diabetic patients. In Yilmaz[28] NLR values were higher in pregnant women with gestational DM compared to pregnant women without gestational DM. NLR value of >2.93 had a low sensitivity of 76% and a higher specificity of 94% and for gestational diabetes. In the study done by Assulyn T *et al,* NLR value of 2.54 had a poor sensitivity of 39.7% and higher specificity of 78.8% with a positive predictive value (PPV) of 45%. Our study had a sensitivity of 70.6% and specificity of 71.9% with a positive predictive value of 84.2% and positive likelihood ratio of 2.51.

CONCLUSIONS

In the current study statistically significant association was found with FBS, PBBS, Proteinuria, HbA1c and NLR values. In diabetic patients, NLR deterioration is associated with poor glycemic control, which increases the importance of hemogram in diabetic patients. In cases in which HbA1c measurement cannot be performed and if the glycemic condition is not evaluated earlier, NLR can be a useful examination. Improvement of NLR after glycemic regulation has suggested that this parameter may be useful in monitoring treatment response. NLR may be useful as an easily measurable, noninvasive, available and cost-effective parameter for the monitoring glycemic control and treatment response in diabetic patients.

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