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Correlation of leucocyte and platelet indices in patients with type 2 diabetes mellitus with microvascular complications at a tertiary care hospital in south India – A prospective cross-sectional study

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Objective. The present study was directed to assess the correlation between leukocyte and platelet indices and microvascular complications in patients with type 2 diabetes mellitus (T2DM).

Methods. A prospective cross-sectional study was conducted between January 2020 and May 2021 at a tertiary healthcare center. Sixty T2DM patients, who fulfilled the inclusion and exclusion criteria, were included into the study and divided into 2 groups: T2DM patients with microvascular complications and T2DM patients without vascular complications. Clinical history was taken and examinations (routine complete blood count) were done to obtain platelet indices, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) were obtained and tabulated. A correlation was statistically analyzed from the obtained data, p value <0.05 was considered to be statistically significant.

Results. From the patients with microvascular complications, 18 cases suffered from retinopathy and nephropathy. Majority of the participants suffered from moderate non-proliferative retinopathy. The creatine median and absolute neutrophil count (ANC) were significantly higher in T2DM patients with microvascular complications ($p<0.0001$ and $p<0.0054$, respectively) compared to T2DM patients without vascular complications. No significant correlation was found between platelet indices, NLR, PLR with regard to fasting blood sugar, post prandial blood sugar, HbA1C in T2DM patients.

Conclusions. Since no significant correlation was found between the different platelet indices and microvascular complications, it is evident that these markers cannot be used as the predictors of microvascular complications in T2DM patients.

Key words: diabetes mellitus, microvascular complications, retinopathy, platelet indices, blood sugar levels

Type 2 diabetes mellitus (T2DM) is a lifestyle and diet related condition gradually becoming popular among children and adolescents. It is characterized by a relative insulin deficiency caused by pancreatic β-cell dysfunction and insulin resistance in target organs (Chatterjee et al. 2017; Huang et al. 2019). T2DM accounts for 90–95% of all cases of diabetes (Pradeepa and Mohan 2017).

T2DM has become a major public health issue with its global adult prevalence rising from 4.7% in 1980 to 8.5% in 2014 (Henning 2018). In 2015, it was found that about 8.8% of the adult population

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was affected by T2DM. It was projected that in 2040, the prevalence of T2DM among the global adult population is expected to be around 10.4%, which accounts for about 642 million diabetic patients (Pradeepa and Mohan 2017).

The microvasculature is affected by chronic intracellular hyperglycemia and genetic predisposition, which can result in complications mainly in kidney function, eyes, and nervous system (Faselis at al. 2020). Nearly 25% of population with T2DM are affected by diabetic nephropathy and retinopathy, another 50% are afflicted by diabetic neuropathy with 35–90% diabetic men showing prevalence of erectile dysfunction. These complications are the results of risk factors such as the duration of T2DM condition along with glycemic index, blood pressure, and lipid control (Faselis at al. 2020).

Diabetes can result in many complications in humans with end-stage renal disease (ESRD) being one of the sequelae of diabetic nephropathy. The diabetic retinopathy being one of the major causes of blindness and diabetic neuropathy being considered a major risk factor for amputation. About a quarter of all newly diagnosed T2DM patients are estimated to have already developed one or more complications of diabetes mellitus (Faselis at al. 2020).

T2DM is also associated with cerebral complications in patients with 2.5-times increased risk of ischemic stroke, 1.5-times increased risk of hemorrhagic stroke, and 1.5-times increased risk of dementia. T2DM patients are also 1.5–2.0 times more likely to suffer from major depression compared to non-diabetic ones (van Sloten et al. 2020).

In the recent decade, the burden of T2DM microvascular complications has exponentially risen with more increase projected. The pathogenesis of most of these complications is not fully understood. A study on sensitive biomarkers is needed for early diagnosis of these microvascular complications, which could help devise interventions to reverse the pathophysiologic mechanisms implicated in the development and progression of these disorders. The present study was conducted to find a correlation between platelet indices, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and microvascular complications in T2DM patients.

Materials and Methods

Subjects. The present study was a prospective cross-sectional study conducted between January 2020 and May 2021 at the Department of General Medicine of a tertiary healthcare center situated in Coimbatore, Tamil Nadu, India. The study was commenced after obtaining ethical clearance from the Institutional Review Board (Ref no: PSG/IHEC/2020/Appr/Exp/019) and informed consent from the study participants.

The inclusion criteria for the present study were: 1) diabetic patients above the age of 18 years, 2) T2DM patients with microvascular complications (retinopathy, neuropathy, nephropathy) and without any vascular complications. The exclusion criteria for the study were: 1) patients aged <18 years, patients with anemia or hematological disorders or active infection or malignancies, patients already on antiplatelet drugs or anticoagulants, immunosuppressant, steroids, 2) patients who received whole blood transfusion in past 2 weeks, patients with renal, cardiac, hepatic failure and 3) patients not willing for to participate in the present study.

Sample size estimation. In study conducted by Jindal et al. 2011, it has been observed that mean of platelet distribution width (PDW) in case and control group was 18.14±3.14% and 15.67±3.77%, respectively, with 95% confidence level, 80% power; the calculated final sample size was 30 for each group.

The participants included were divided into 2 groups: 1) T2DM patients with microvascular complications and 2) T2DM patients without vascular complications. Sample size was calculated to be 60 with each group including 30 patients.

Clinical history was taken and examinations were done to obtain data regarding demographic details and complications. Complete blood count was done as a part of routine investigations for all the participants. Platelet indices, NLR, PLR and LMR, were obtained from the complete blood count report and tabulated for the two study groups. Correlations were assessed by statistical analysis of the data obtained.

Statistical analysis. Data analysis was done using R i386 3.6.3. Continuous variables were represented as mean±standard deviation. Categorical variables were represented by frequency tables. Continuous data were compared using t-test, Welch's t-test, and Mann-Whitney U-test. Shapiro Wilk test was used to test the normality and Levene test was used to test the equal variance assumption. Correlation between continuous data was compared using Spearman rank correlation. A p value <0.05 was considered statistically significant.

Results

A total of 60 subjects consisting of 30 cases in each group were included in the study. It was observed

that most cases (60%) had both retinopathy and nephropathy. In 30 cases with microvascular complications, the majority of participants (70%) had diabetic retinopathy, of which 43.33% of participants suffered from moderate non-proliferative diabetic retinopathy (Table 1). The mean age of the patients was 58 and 54.4 and female to male ratio 1.3:1.7 and 1: 1.5 in the group 1 and 2, respectively.

Using one-tailed Mann-Whitney U-test, it was found that median of creatinine was significantly higher in T2DM patients with microvascular complication (1.86±1.62 mg/dL) than in T2DM patients without microvascular complications (0.78±0.19 mg/dL) ($p<0.0001$). Using one-tailed Welch's t-test, it was concluded that mean of absolute neutrophil count (ANC) was significantly higher in T2DM patients with microvascular complication (6.78±3.44) compared to T2DM patients without microvascular complications (4.92±1.71) ($p=0.005$) (Table 2).

Using Spearman's rank correlation, it was found that there is no significant correlation between fasting blood sugar (FBS) and platelet indices, like mean platelet volume (MPV) ($p=0.1465$), plateletcrit ($p=0.5403$), PDW ($p=0.7339$) as well as NLR (0.1541), PLR ($p=0.6187$), LMR ($p=0.9087$), creatinine ($p=0.6718$), ANC ($p=0.5424$), absolute lymphocyte count (ALC) ($p=0.3264$), absolute monocyte count (AMC) ($p=0.8137$) and platelet ($p=0.5204$) in T2DM patients.

Similarly, it was concluded that there is no significant correlation between post prandial blood sugar (PPBS) among T2DM patients and platelet indices, like MPV ($p=0.8472$), plateletcrit ($p=0.7071$), PDV ($p=0.8571$) as well as NLR (0.3944), PLR ($p=0.6965$), LMR ($p=0.5201$), creatinine ($p=0.8531$), ANC ($p=0.1582$), ALC ($p=0.7869$), AMC ($p=0.9909$) and platelet ($p=0.4285$). There was also no significant correlation between HbA1C in T2DM patients and platelet indices, like MPV ($p=0.9877$), plateletcrit ($p=0.8257$), PDW ($p=0.5647$) as well as NLR (0.7305), PLR ($p=0.4925$), LMR ($p=0.0676$), creatinine ($p=0.7046$), ANC ($p=0.7924$), ALC ($p=0.8567$), AMC ($p=0.2082$) and platelet ($p=0.2785$) (Table 3).

Discussion

A substantial global burden of microvascular complications is faced by patients with T2DM relatively early in the disease process (Kosiborod et al. 2018). A pro-inflammatory microenvironment is created due to diabetes and hyperglycemia and this progresses to microvascular complications such as neuropathy, nephropathy and retinopathy. A potential initiator for this condition is the diet-induced insulin resistance in T2DM and this can further increase adipokines and generate a chronic low-grade inflammatory state (Nguyen et al. 2012). These findings highlight an importance to find biochemical markers which can help assess development and extent of microvascular complications in diabetic patients.

In the present study, it was observed that a large portion of cases suffered from both retinopathy and nephropathy. In those with microvascular complications, majority suffered from diabetic retinopathy and mostly of moderate NPDR type. This was in disagreement with the results of a study of Faselis et al. (2020), who have concluded that diabetic neuropathy was encountered in nearly 50% of the diabetic population and diabetic nephropathy and retinopathy affected only close to 25% of patients with T2DM. According to a study of Kosiborod et al. (2018), common microvascular complications included peripheral

Table 1
Distribution of subjects with complications and retinopathy in case group (n=30)

Factor	Sub-category	Count (%)
Complication	Nephropathy	1 (3.33%)
	Neuropathy	7 (23.33%)
	Neuropathy, Nephropathy	1 (3.33%)
	Retinopathy, Nephropathy	18 (60%)
	Retinopathy, Neuropathy, Nephropathy	3 (10%)
Severity of retinopathy	Mild non-proliferative diabetic retinopathy (NPDR)	3 (10%)
	Moderate NPDR	13 (43.33%)
	Severe NPDR	3 (10%)
	Proliferative diabetic retinopathy (PDR)	2 (6.67%)
	No retinopathy	9 (30%)

Table 2
Association of blood sugar values with cases among study participants

Parameter	Case group	Control group	p-value
FBS (mg/L)	175.00±85.43	162.67±47.77	0.4929[T]
PPBS (mg/dL)	286.63±135.21	259.57±95.09	0.3735[T]
HbA1c (%)	9.96±2.82	9.17±2.29	0.2403[T]
Creatinine (mg/dL)	1.86±1.62	0.78±0.19	<0.0001[MA]
Urine PCR	4.31±4.98	-	
ANC (x103/µl)	6.78±3.44	4.92±1.71	0.0054[WA]
ALC (x103/µl)	1.81±0.79	2.03±1.14	0.4024[WT]
AMC ($x10^3$/µl)	0.64±0.47	0.62±0.30	0.6394[M]
Platelet ($x10^3$/µl)	281.03±93.98	268.1±103.36	0.6140[T]
NLR	5.28±5.25	3.53±2.47	0.258[M]
LMR	3.39±1.49	3.51±1.55	0.7785[T]
PLR	211.33±193.96	166.66±78.15	0.9058[M]
MPV	8.32±1.23	8.28±0.81	0.9019[WT]
Plateletcrit (%)	0.23±0.08	0.23±0.09	0.9467[T]
PDW (%)	17.22±0.75	16.91±0.44	0.0539[WT]

Abbreviations: ALC – absolute lymphocyte count; AMC – absolute monocyte count; ANC – absolute neutrophil count; FBS – fasting blood sugar; HbA1c – glycosylated hemoglobin; LMR – lymphocyte-monocyte ratio; MPV – mean platelet volume; NLR – neutrophil-lymphocyte ratio; PCR – protein/creatinine ratio; PDW – platelet distribution width; PLR – platelet-lymphocyte ratio; PPBS – post-prandial blood sugar. Case group – type2 diabetes mellitus (T2DM) patients with microvascular complication; Control group – T2DM patients without microvascular complication. Data were statistically analyzed by t-test ([T]), Welch's t-test ([WT]), Mann-Whitney U test ([M]) and one-tailed test ([A]).

Table 3
Correlation of platelet indices, neutrophil-lymphocyte ratio, platelet lymphocyte ratio with fasting blood sugar, post-prandial blood sugar, HbA1c in type 2 diabetes mellitus patient

Parameter	FBS		PPBS		HbA1c	
	rho	p-value	rho	p-value	rho	p-value
MPV	0.19	0.1465	0.03	0.8472	0	0.9877
Plateletcrit	–0.08	0.5403	0.05	0.7071	0.03	0.8257
PDW	–0.04	0.7339	0.02	0.8571	–0.08	0.5647
NLR	0.19	0.1541	0.11	0.3944	0.05	0.7305
PLR	0.07	0.6187	0.05	0.6965	0.09	0.4925
LMR	–0.02	0.9087	0.08	0.5201	0.24	0.0676
Creatinine	0.06	0.6718	–0.02	0.8531	0.05	0.7046
ANC	0.08	0.5424	0.18	0.1582	0.03	0.7924
ALC	–0.13	0.3264	0.04	0.7869	–0.02	0.8567
AMC	–0.03	0.8137	0	0.9909	–0.16	0.2082
Platelet	–0.08	0.5204	0.1	0.4285	0.14	0.2785

Abbreviations: ALC – absolute lymphocyte count; AMC – absolute monocyte count; ANC – absolute neutrophil count; FBS – fasting blood sugar; HbA1c – glycosylated hemoglobin; LMR – lymphocyte-monocyte ratio; MPV – mean platelet volume; NLR – neutrophil-lymphocyte ratio; PDW – platelet distribution width; PLR – platelet-lymphocyte ratio; PPBS – post-prandial blood sugar; rho - spearman rank correlation.

neuropathy (7.7%), chronic kidney disease (5.0%), and albuminuria (4.3%). This difference can be attributed to the low sample size and single center nature of the present study.

The HbA1c levels were not found to be significantly different between the two groups in the present study. This is in disagreement with the results of the study conducted by Woo et al. (2011), who have assessed significantly elevated HbA1c levels (p=0.0003) in patients with diabetic retinopathy group compared to the group without any complications. The results of the present study are also in contrast with the Wisconsin Epidemiologic Study demonstrating that in patients with diabetes, higher baseline hemoglobin A1c (HbA1c) levels correlated with increased incidence of retinopathy, progression of retinopathy, and progression of proliferative retinopathy (Klein et al. 1984a,b). This could be explained by microvascular complications occurring as a consequence of a longer duration of diabetic condition.

The present results showed that the creatinine level was significantly higher in the T2DM patients with microvascular complication compared to T2DM patients without microvascular complications. These results are also in agreement with those of a previous study, in which serum creatine levels were higher in the diabetic retinopathy group than in the group without diabetic retinopathy but this difference was not statistically significantly (p=0.4279) (Woo et al. 2011). This could be explained by the nephropathic complications that are attributed to the diabetic condition in patients.

It has also been found that the ANC mean was significantly higher in the T2DM patients with microvascular complication in relation to T2DM patients without microvascular complications. This is in agreement with the results of a previous study (Woo et al. 2011), which has shown that the mean ANC was significantly higher (p<0.05) in the diabetic retinopathy group than in the group without retinopathy.

Platelet indices, like MPV, PDW, were not found to be associated with the occurrence of microvascular complications in the present study. These results are similar to those of a study conducted by Shilpi and Potekar (2018), in which MPV and PDW in diabetic patients were higher in those with complications compared to those without complications, but these differences were not statistically significant. The results of the present study are in contrast to those obtained by Jindal et al. (2011), in which PDW and MPV were found to be higher in diabetics with microvascular complications compared to those without complications (p<0.05). This study has concluded that PDW could be used for the classification of diabetic patients (Jindal et al. 2011). These results were also in disagreement with the results of other studies, in which the increase in MPV and PDW was significantly higher in diabetics with microvascular complications compared with those without complications. A platelet dysfunction showed a positive association with nephropathy, HbA1c, retinopathy and neuropathy (Walinjkar et al. 2019; Taderegew et al. 2021). These studies had a much larger sample size compared to this study, which could explain the difference in results

A previously conducted review had shown that MPV changes were observed with increased levels in cardiovascular diseases, cerebral stroke, respiratory diseases, chronic renal failure, intestine diseases, rheumatoid diseases, diabetes, and various cancers. Decreased MPV have been noted in tuberculosis during disease exacerbation, ulcerative colitis, SLE in adult, and different neoplastic diseases (Korniluk et al. 2019). This adds to evidence that MPV could be used as a test to assess development of inflammatory complications.

In the present study, the platelet count and plateletcrit levels were found to be higher in the group with microvascular complications, but this difference was not statistically significant. These results are in disagreement with the study of Qian et al. (2021), where the lower platelet and plateletcrit levels were associated with a presence of neuropathy in patients with T2DM. This could be explained by the fact that the majority of the participants in the present study suffered from retinopathy, with the conclusion that the pathogenesis of both complications shows different alterations in biochemical parameters.

The present results showed that there was no significant correlation between platelet indices, NLR as well as PLR and FBS, PPBS, HbA1C in T2DM patients. These results of the present study are in contrast to those of Wang et al. (2021), who have concluded that the neutrophil count in diabetic patients was a significant predictor of HbA1c levels (p=0.010). This is also in contrast with the pathology of diabetes, which includes hyperglycemic condition in diabetic patients, but could be explained by the included patients having their diabetic parameters under control.

Recently, the management of microvascular complications associated with diabetes has been focused on the primary prevention by promoting healthy eating habits, exercise and physical activity, and tobacco abstinence from an early age. Health

care professionals address the risk factors specifically aiming for tight glycemic and blood pressure control with judicious use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB)s, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, statins, and fibrate therapies. The advent of biomarker associated research would provide a manner of treatment of the different complications, which is more targeted (Crasto et al. 2021). According to a recent study, microalbuminuria is considered an early marker of diabetic nephropathy and can be used for routine screening, but the renal damages may also occur without microalbuminuria (Thipsawat 2021). The same parameter was not included in the present study. Microvascular complications have also been associated with an increased risk of cardiovascular disease and heat failure, not only in patients with diabetes, but also in the general population and even more when several complications co-exist (Avogaro and Fadini 2019).

The strength of the present study is that none of the included patients had missing data and that biochemical parameters were compared between patients with and without microvascular complications. The limitation of the study lies in the small sample size compared to other studies, which have assessed different aspects of diabetic condition. The clinical implications of the present study are that biochemical parameters can be used to assess the development and extent of microvascular complications in patients suffering from T2DM. The present study necessitates the conduction of large-scale studies, which can help in finding a cost-effective manner to assess microvascular complications in diabetic patients.

From the present study, we can conclude that there is no significant correlation between NLR, LMR, PLR, MPV, plateletcrit, PDW and diabetic patients with microvascular complications. Further studies could help in revealing biochemical markers, which can provide data on the development and extent of microvascular changes in patients suffering from T2DM.

Conflicts of interest: *The authors declare no conflicts of interest.*

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