doi: 10.21860/medflum2024_316191

Red Cell Distribution Width and Platelet Indices as Inflammatory Parameters in Type 2 Diabetic Patients with Kidney Dysfunction

Širina distribucije eritrocita i trombocitni indeksi kao inflamatorni parametri kod pacijenata sa šećernom bolesti tipa 2 i disfunkcijom bubrega

Almir Fajkić[1*], Rijad Jahić[2], Avdo Kurtović[3], Lamija Mlačo[4], Amela Dervišević[4], Hana Bašić[5], Layan Mattar[5], Fatka Kovačević[5], Khelle Lama[5], Malik Ejubović[6], Orhan Lepara[4]

[1] University of Sarajevo, Faculty of Medicine, Department of Pathophysiology, Sarajevo, Bosnia and Herzegovina

[2] General Hospital "Prim. Dr. Abdulah Nakas", Sarajevo, Bosnia and Herzegovina

[3] Clinical Center University of Tuzla, Tuzla, Bosnia and Herzegovina

[4] University of Sarajevo, Faculty of Medicine, Department of Human Physiology, Sarajevo, Bosnia and Herzegovina

[5] University of Sarajevo, Faculty of Medicine, Sarajevo, Bosnia and Herzegovina

[6] Cantonal Hospital Zenica, Department of Internal Medicine, Zenica, Bosnia and Herzegovina

[*]**Corresponding author:**
Almir Fajkić, M.D., Ph.D.
University of Sarajevo, Faculty of Medicine, Department of Pathophysiology
Čekaluša St. 90, 71000 Sarajevo, Bosnia and Herzegovina
E-mail: almir.fajkic@mf.unsa.ba

Abstract. ***Aim:*** To assess Red blood cell Distribution Width (RDW) and platelet indices values in patients with type 2 diabetes mellitus (T2DM) and to verify its association with kidney dysfunction (KD). ***Patients and Methods:*** A cross-sectional study included 149 T2DM subjects divided into two groups with (T2DM – KD; n=52) and without (T2DM-nKD; n=97) presence of kidney dysfunction and 30 healthy subjects. White Blood Cells (WBC) count, C-reactive protein (CRP), fibrinogen, RDW, platelet indices, urea, and creatinine, were measured in all participants. Kidney function was evaluated by the estimated glomerular filtration rate (eGFR) calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula. ***Results:*** T2DM-KD subjects showed statistically significantly higher values of the parameters RDW ($p<0.01$), Mean Platelet Volume – MPV ($p<0.01$), Platelet Distribution Width-PDW ($p<0.01$), Platelecrit-PCT ($p<0.01$), and Platelet Mass Index-PMI ($p<0.01$) compared to T2DM-nKD subjects, and statistically significantly lower values of the WBC count in T2DM-KD subjects compared to subjects suffering from T2DM without kidney dysfunction ($p<0.01$). ROC curve analysis revealed that RDW (sensitivity of 80.8%, specificity of 78.3%), MPV (sensitivity of 75%, specificity of 78.4 %), and PDW (sensitivity of 80.8%, specificity of 83.5%) could be used as markers in distinguishing between T2DM subjects with and without kidney dysfunction. ***Conclusion:*** This study confirms the reliability of the RDW,MPV, and PDW as simple, low cost and useful markers in distinguishing between T2DM subjects with and without kidney dysfunction.

Keywords: Blood Platelets; Diabetes Mellitus, Type 2; Erythrocytes; Renal Insufficiency

Sažetak ***Cilj***: Evalvirati vrijednosti širine raspona veličine eritrocita (RDW) i trombocitnih indeksa kod pacijenata sa šećernom bolesti tipa 2 (T2DM) i potvrditi njihovu povezanost s disfunkcijom bubrega (KD). ***Pacijenti i metode***: Presječna studija uključila je 149 pacijenata sa šećernom bolesti tipa 2 podijeljenih u dvije grupe – pacijente s bubrežnom disfunkcijom (T2DM-KD; n = 52) i bez nje (T2DM-nKD; n = 97), te 30 zdravih ispitanika. Broj leukocita (WBC), C-reaktivni protein (CRP), fibrinogen, RDW, indeksi trombocita, urea i kreatinin izmjereni su kod svih participanata. Kao mjera funkcije bubrega korištena je procijenjena brzina glomerularne filtracije (eGFR) izračunata korištenjem formule MDRD (*Modification pf Diet in Renal Disease*). ***Rezultati***: Pacijenti s T2DM-KD pokazali su statistički značajno veće vrijednosti parametara RDW ($p < 0,01$), srednji volumen trombocita – MPV ($p < 0,01$), širinu distribucije volumena trombocita – PDW ($p < 0,01$), trombokrit – PCT ($p < 0,01$) i indeks mase trombocita – PMI ($p < 0,01$) te statistički značajno niže vrijednosti WBC u odnosu na pacijente koji boluju od T2DM bez bubrežne disfunkcije ($p < 0,01$). Analiza ROC krivulje otkrila je da se RDW (granični nivo 53,5, senzitivnost 80,8 %, specifičnost 78,3 %), MPV (granični nivo 11,55, senzitivnost 75 %, specifičnost 78,4 %) i PDW (granični nivo 15,65,

senzitivnost 80,8 %, specifičnost 83,5 %) mogu koristiti kao markeri u razlikovanju pacijenata sa šećernom bolesti tipa 2, onih s bubrežnom disfunkcijom i onih bez nje. ***Zaključak***: Ova studija potvrđuje pouzdanost RDW, MPV i PDW kao jednostavnih, jeftinih i korisnih markera u razlikovanju pacijenata sa šećernom bolesti tipa 2, s bubrežnom disfunkcijom i bez bubrežne disfunkcije.

Ključne riječi: eritrociti; insuficijencija bubrega; šećerna bolest tipa 2; trombociti

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a complex, metabolic disease characterized by chronic hyperglycaemia that is associated with long-term macro- and microvascular complications especially in the eyes, kidneys and nerves[1, 2]. Kidney dysfunction (KD), which develops due to long-term exposure to hyperglycaemia, is one of the main diabetic complications. The main mechanisms that lead to the development of diabetic kidney damage include oxidative stress, changes in kidney blood vessels, protein absorption, and inflammation[3, 4].

Inflammatory mechanisms contribute to the development of KD in subjects with diabetes through several pathways and represent one of the central mechanisms. For this reason, researchers have shown great interest in the inflammatory parameter as a possible biomarker of the development of kidney dysfunction in diabetes. However, the results of previous studies are inconsistent regarding the role of classical inflammatory parameters as potential markers of KD[5].

Increased scientific efforts have been made to use nonstandard inflammatory markers that can be better associated with kidney dysfunction. Since inflammation significantly affects blood cells such as red blood cells and platelets, novel research has focused on their parameters that may be the answer to the complex interaction between inflammation and diabetic kidney dysfunction.

Hyperglycaemia increased glycation and oxidative stress in T2DM can also decrease erythrocyte deformability. Decrease erythrocyte deformability leads to volume variability[6]. Red cell distribution width (RDW) is a measure of red blood cell volume variability and is considered as a novel inflammatory marker associated with many conditions, including T2DM. Previous studies have shown that higher RDW values are negatively correlated with estimated glomerular filtration rate (eGFR) and positively correlated with heavier proteinuria and lower levels of albumin[6–8].

Besides these effects, T2DM is considered a "prothrombotic state" owing to endothelial and pericyte injury. Many studies have shown that endothelial dysfunction is associated with increased mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P LCR). These parameters are considered indicators of increased platelet activity and potential biomarkers for diabetic complications[2].

Kidney dysfunction, which develops due to long-term exposure to hyperglycaemia, is one of the main diabetic complications. The main mechanisms that lead to the development of diabetic kidney damage include oxidative stress, changes in kidney blood vessels, protein absorption, and inflammation.

The main aim of our study is to assess novel inflammatory parameters – RDW and platelet indices values in subjects with T2DM and to verify its association with KD.

PATIENTS AND METHODS

Subjects and study design

The cross-sectional study was conducted among 149 subjects with T2DM who were admitted, between January 2017 and January 2020, to Family Medicine and Endocrine counselling in the area of Health centres of Sarajevo Canton. Subjects with any of the following diagnoses or conditions were excluded from the study: haemoglobin (Hb) in females with Hb<100 g/l and males with Hb<120 g/l, subjects with coronary artery disease, hepatic, or kidney failure; thrombocytosis and thrombocytopenia; evidence of coronary heart disease; autoimmune disease; urinary tract infection; or a history of alcohol abuse and medication with antiplatelet drugs.

The control group consisted of 30 healthy subjects without a family history of coronary heart diseases, hypertension, or autoimmune diseases

and with normal kidney and hepatic functions, and without present platelet disorders. None of the control subjects had received any medication.

Written informed consent for inclusion in the study was obtained from all subjects and healthy controls.

The study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, University of Sarajevo (02-3-4-4338) according to the recommendations contained in the Declaration of Helsinki on Biomedical Research Involving Human Subjects as revised in 2013.

In the search for potential biomarkers among standard laboratory tests, PDW, MPV, and RDW were found to be reliable inflammatory biomarkers for KD in T2DM subjects in terms of sensitivity and specificity.

Methods

Kidney function was evaluated by the estimated glomerular filtration rate (eGFR) calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula:

$$eGFR\ (mL/min/1.73\ m^2) = 175 \times [Serum\ Creatinine\ (\mu mol/L) \times 0.0113]^{-1.154} \times Age\ (years)^{-0.203}\ (\times 0.742\ if\ female)$$ [9].

Kidney dysfunction was defined as an eGFR < 60 ml/minute/1.73 m^2 [10]. Based on the eGFR value, T2DM subjects were divided into two groups: T2DM subjects with kidney dysfunction (T2DM-KD group; n=52) and T2DM subjects without kidney dysfunction (T2DM-nKD group; n=97).

The systolic and diastolic blood pressures (BP) were measured using a calibrated standard mercury sphygmomanometer in a sitting position after a 5-min rest.

Peripheral venous blood samples were collected, using the vacutainer technique, in the morning after the overnight fast, after a 30-min rest from all subjects and controls.

Serum glucose levels and kidney function tests were made on Beckman coulter chemistry analyzer AU480. Serum CRP concentration was measured by the immunoturbidimetric assay (Beckman Synchron LX System). Plasma fibrinogen was measured by the standard clot method using the BCS Coagulation System (Dade Behring).

White Blood Cells (WBC) count, RDW, the platelet count (PLT), and platelet indices were determined as part of the automated complete blood count (CBC) on an automatic haematology analyzer (CELL-DYN Ruby; Abbott Laboratories, USA).

The Platelet Mass Index (PMI) value was calculated by multiplying the platelet count by the mean platelet volume[10].

From obtained values of RDW and PLT, the Red Blood Cell Distribution Width-to-Platelet Ratio (RPR) was calculated as RPR = RDW (%)/platelet count (10^9/L)[11].

Statistical analysis

Statistical analysis was performed by two different programs, MS Excel (Microsoft Office Excel 2010) and SPSS (SPSS-Statistical Package for 27 Social Sciences) version 22.0. The Kolmogorov-Smirnov and Shapiro-Wilk tests, depending on the sample size, were used to assess the normality of variable distribution. The mean value (X) and standard deviation (SD) for continuous independent variables that followed the normal distribution were determined, and the median and interquartile range for independent continuous variables did not follow the normal distribution. The Student t-test tested the significance of the difference for the independent variables that followed the normal distribution. In contrast, the Mann – Whitney U-test tested the significance of the difference for the independent variables that did not follow the normal distribution. Correlations between continuous variables were assessed using Pearson's or Spearman's correlation coefficient. To determine the accuracy and respective cut-off values for differentiating subjects with T2DM-KD subjects from T2DM-nKD subjects, the Receiver Operating Characteristic (ROC) curves and their corresponding areas under the curve (AUC) were used. The accuracy rate for ROC curves was calculated with a 95% confidence interval (95% CI). A $p<0.05$ was considered statistically significant.

RESULTS

One hundred seventy-nine (179) subjects were evaluated in our study, 149 were T2DM subjects

Table 1. Demographic data, clinical and biochemical parameters of the study population

Variables		T2DM group (n=149)	Control group (n=30)	p
n (%)	Males	76 (51%)	15 (50%)	0.892
	Females	73 (49%)	15 (50%)	0.790
(Years)	Age	50 (47 – 55)	49 (45 – 52)	0.111
(mmol/L)	Glucose	6.2 (5.8 -6.6)	5.2 (5.17 – 5.4)	0.000**
(mmHg)	SAP	130 (120 – 140)	120 (120 – 120)	0.000**
	DAP	80 (80 – 100)	70 (70 – 80)	0.000**
(mmol/L)	Serum urea	7.7 (6.7 – 8.95)	6 (5 – 6.95)	0.000**
(µmol/L)	Creatinine	89 (79.5 – 98)	81.5 (73.75 – 88.5)	0.004**
	eGFR	67.3 (58.25 -78.4)	108 (97 – 113)	0.000**
(x 10^9)	WBC	8.17 ± 4.6	7.55 ± 1.17	0.267
(g/L)	CRP	3.69 ± 1.07	3.81 ± 0.64	0.554
	Fibrinogen	3.2 (2.7 -3.7)	2.9 (2.6 -3.5)	0.111
(%)	RDW	52 (47 – 58)	43 (38 – 47)	0.000**
(x 10^9)	PLT	288 (263 – 340)	326.5 (278 – 356.75)	0.02*
(10^{-15}l)	MPV	10.9 (9.6 – 12.8)	9.3 (8.37 – 10.32)	0.000**
(%)	PDW	14.8 (13.8 – 16.65)	11.7 (10.87 – 12.98)	0.000**
	PCT	0.26 (0.21 – 0.28)	0.23 (0.18 – 0.26)	0.001**
	PMI	3.11 (2.64 – 3.93)	3.03 (2.59 – 3.38)	0.131
	RPR	17.1 (15.27 – 20.64)	13.11 (11.86 – 15.34)	0.000**

Results are presented as: mean ± SD, or median with interquartile range (25–75 percentile); n = number of subjects; T2DM – Type 2 Diabetes Mellitus; eGFR (estimated glomerular filtration rate); CRP – C reactive protein; WBC – White Blood Cells count; PLT – Platelet count; RDW – Red Blood Cell Distribution Width; MPV– Mean Platelet volume; PDW – Platelet distribution width; PCT – Platelecrit; PMI-Platelet Mass index; RPR – Red Blood Cell Distribution Width-to-Platelet Ratio; *p<0.05;**p<0.01

and 30 were healthy controls. There were no significant differences between T2DM and healthy controls concerning gender (p=0.892 for male; p= 0.790 for female) or age (p=0.111). Serum urea and creatinine level were significantly higher in T2DM subjects than in the control group (p<0.01). A control group of subjects had a significantly higher value of eGFR than T2DM subjects (p<0.01). Additionally, subjects in the T2DM group had significantly higher RDW, PLT, MPV, PDW, and PCT values (p=0.000, p=0.02, p=0.000, p=0.000, p=0.001, respectively) than in the control group. However, WBC, CRP, fibrinogen, and PMI did not differ significantly between the groups (p=0.267, p=0.554, p=0.111, p=0.131 respectively) (Table 1).

Among T2DM subjects, 52 (34.89%) had KD, and 97 (65.11%) did not have KD. Subjects in the T2DM-KD group had significantly higher values of serum urea, creatinine, RDW, MPV, PDW, PCT, and PMI (p<0.01) than in the T2DM-nKD group. On the other side, the value of WBC in T2DM-KD subjects was significantly lower than in the T2DM-nKD group (p<0.01). The median serum level of CRP, fibrinogen, and platelet count were similar in both groups, without significant difference (p=0.445, p=0.213, p=0.382, respectively) (Table 2).

In T2DM subjects with KD, a statistically significant negative correlation was shown between the parameters RDW (rho=-0.408, p=0.003), MPV (rho=-0.357, p=0.009), PDW (rho=-0.560, p<0.001) with the eGFR parameter and a statistically significant positive correlation of the WBC (rho=0.403, p=0.003) and CRP (rho=0.477; p=0.006) parameters with the eGFR parameter. In addition, a statistically significant negative correlation was shown between the parameters CRP (r=-0.358, p=0.009) and platelet count (rho= -0.280, p=0.044) with the parameter serum urea,

Table 2. Clinical and biochemical parameters in T2DM-KD and T2DM-nKD group

Variables		T2DM-KD (n=52)	T2DM-nKD (n=97)	p
(mmol/l)	Serum urea	8.75 (7.55 – 10.4)	7.4 (6 – 8.2)	0.000***
(µmol/L)	Creatinine	101 (95 – 111)	81 (75.5 – 89)	0.000***
	eGFR	56.25 (53.45 – 58.67)	74.9 (67.65 – 82.95)	0.000***
(g/L)	CRP	4.073 ± 1.04	3.48 ± 1.04	0.445
	Fibrinogen	3.35 (2.9 – 3.7)	3.27 (2.7 – 3.5)	0.213
(%)	RDW	60 (57 – 69.75)	48 (45 – 52.5)	0.000***
(x 10^9)	PLT	297 (260 – 353.5)	296 (265 – 320)	0.382
(10^{-15})	MPV	13.2 (11.55 – 13.9)	10.4 (9 – 11.5)	0.000***
(%)	PDW	17.2 (15.9 – 18.5)	14.4 (13.5 – 15.1)	0.000***
	PCT	0.28 (0.23 – 0.31)	0.25 (0.21 – 0.27)	0.000***
	PMI	3.71 (3.08 – 4.53)	2.96 (2.52 – 3.48)	0.000***
	RPR	20.35 (16.91 – 24.49)	16.38 (14.83 – 18.96)	0.000***

Results are presented as: mean ± SD, or median with interquartile range (25–75 percentile); n = number of subjects; T2DM-KD – Type 2 Diabetes Mellitus with Kidney Dysfunction; T2DM-nKD – Type 2 Diabetes Mellitus without Kidney Dysfunction; eGFR – estimated glomerular filtration rate; CRP – C reactive protein; WBC-White Blood Cells count; PLT – Platelet count; RDW – Red Blood Cell Distribution Width; MPV-Mean Platelet volume; PDW – Platelet distribution width; PMI – Platelet Mass index; PCT – Plateletcrit; RPR – Red Blood Cell Distribution Width-to-Platelet Ratio; ***p<0.001

Table 3. Correlation between the haematological, biochemical and kidney function parameters in T2DM KD subjects

Variables		Creatinine	Serum urea	eGFR
(x 10^9)	WBC	rho=-0.120	rho=-0.186	rho=0.403**
(g/L)	CRP	r=0.107	r=-0.358**	r=0.477**
	FIBRINOGEN	r=0.139	r=-0.018	r=0.157
(%)	RDW	rho=-0.006	rho=0.080	rho=-0.408**
(x 10^9)	PLT	rho=0.079	rho=-0.280*	rho=0.067
(10^{-15})	MPV	rho=0.047	rho=0.033	rho=-0.357**
(%)	PDW	rho=-0.140	rho=0.304*	rho=-0.560**
	PCT	rho=-0.066	rho=0.025	rho=-0.233
	PMI	rho=0.115	rho=-0.128	rho=-0.002

rho= Spearman's coefficient; r – Pearson's coefficient; eGFR (estimated glomerular filtration rate); CRP – C reactive protein; WBC – White Blood Cells count; PLT – Platelet count; RDW – Red Blood Cell Distribution Width; MPV – Mean Platelet volume; PDW – Platelet distribution width; PCT – Plateletcrit; PMI – Platelet Mass index; *<0.05; **p<0.01

as well as a statistically significant negative correlation between the parameter PDW (rho=0.304; p=0.029) and serum urea (Table 3).

The ROC curve for WBC, CRP, RDW, MPV, PDW, PCT, and PMI value in the total sample of T2DM-KD vs T2DM-nKD showed a significant area under the curve. ROC curve analysis revealed that RDW (cut-off level of 53.5, with a sensitivity of 80.8%, specificity of 78.3%), MPV (cut-off level of 11.55, with a sensitivity of 75%, specificity of 78.4 %), and PDW (cut-off level of 15.65, with a sensitivity of 80.8%, specificity of 83.5%) could be used as markers of kidney dysfunction in T2DM subjects (AUC=0.879, p<0.01), and (AUC=0.830, p<0.01) (AUC=0.874, p<0.01) (Figure 1, Table 4).

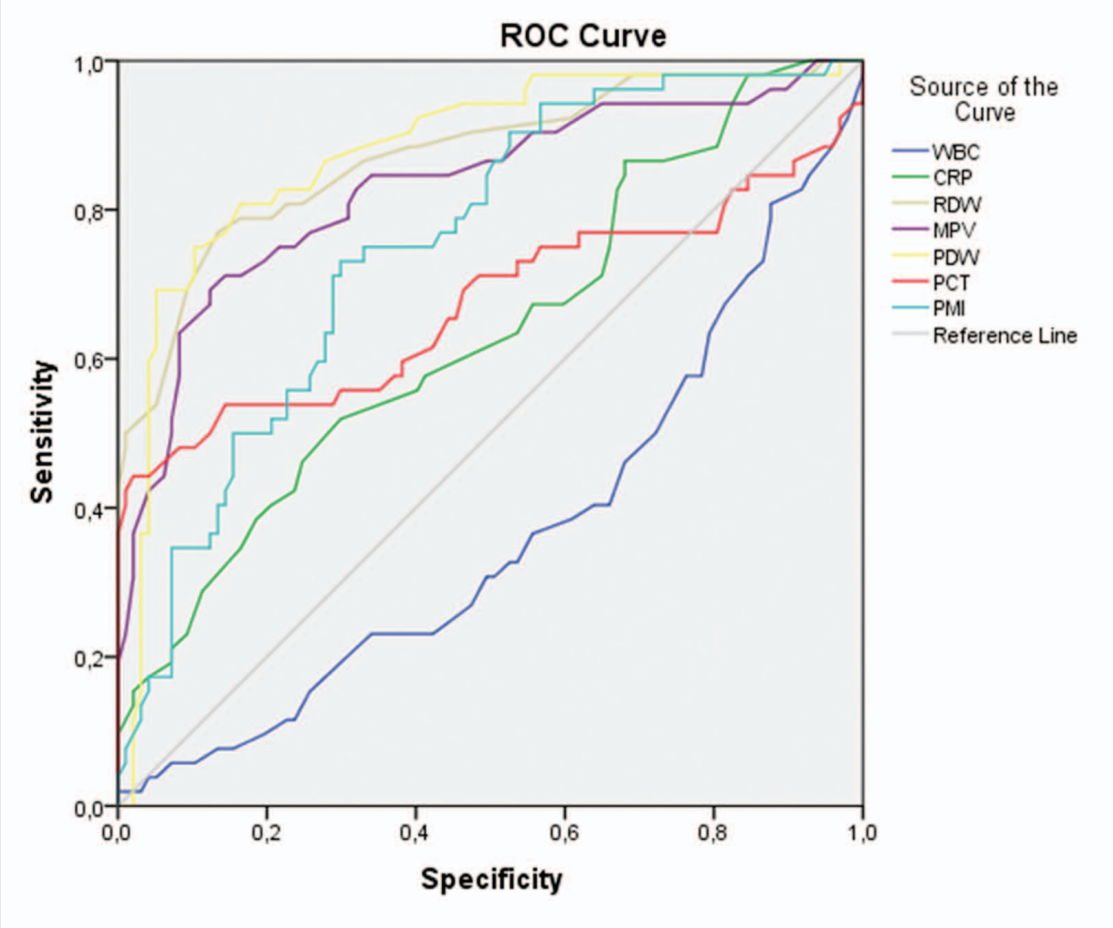

Figure 1. Receiver operating characteristic (ROC) curve of the WBC, CRP, RDW, MPV, PDW, PCT and PMI in differentiating between T2DM-KD (type 2 diabetes mellitus with kidney dysfunction) and T2DM-nKD (type 2 diabetes mellitus without kidney dysfunction) subjects. WBC – White Blood Cells count; CRP – C reactive protein; RDW – Red Blood Cell Distribution Width; MPV – Mean Platelet volume; PDW – Platelet distribution width; PCT – Platelecrit; PMI – Platelet Mass index

Table 4. The optimal cut-off area under the curve with 95% confidence interval (AUC, 95%CI), sensitivity (SEN), and specificity (SPE) of the WBC, CRP, RDW, MPV, PDW, PCT, PMI in differentiating between T2DM-KD (type 2 diabetes mellitus with kidney dysfunction) and T2DM-nKD (type 2 diabetes mellitus without kidney dysfunction) subjects

The variable and cut-off value	AUC (95%CI)	SEN	SPE	p
WBC (7.0)	0.366 (0.272 – 0.481)	57.7	23.7	0.007**
CRP (3.75)	0.634 (0.539 – 0.728)	57.7	58.8	0.007**
RDW (53.5)	0.874 (0.810 – 0.937)	80.8	78.3	0.000**
MPV (11.65)	0.830 (0.756 – 0.904)	75	78.4	0.000**
PDW (15.65)	0.879 (0.817 – 0.940)	80.8	83.5	0.000**
PCT (0.25)	0.673 (0.568 – 0.779)	71.2	52.5	0.000**
PMI (3.25)	0.753 (0.674 – 0.832)	71.2	71.1	0.000**

WBC – White Blood Cells count; CRP – C reactive protein ; RDW – Red Blood Cell Distribution Width; MPV – Mean Platelet volume; PDW – Platelet distribution width; PCT – Platelecrit; PMI – Platelet Mass index; AUC – area under the curve; CI – confidence interval; SEN – sensitivity; SPE – specificity; ** p<0.01

DISCUSSION

This study aimed to clarify the potential role of novel inflammatory parameters, RDW and platelet indices values, in subjects with T2DM in a diagnosis of KD. An early diagnosis of diabetes and diabetic complications represents a true challenge for modern medicine describing those problems through the availability of resources represented as a decline in eGFR[12]. In that context, standard blood tests especially related to inflammatory processes with the role of biomarkers represent an enormous power for a timely diagnosis of diabetic complications because microalbuminuria, as a cornerstone finding of a decline in kidney function, was absent in 30% of subjects with T2DM and low kidney function regarding the cut-off value of eGFR[13].

In the search for potential biomarkers among standard laboratory tests, PDW, MPV, and RDW were found to be reliable inflammatory biomarkers for KD in T2DM subjects in terms of sensitivity and specificity.

When it comes to platelet indices, our results agree with previous research. Mi et al. found out that PDW had a sensitivity of 80% and specificity of 97.8% in the diagnosis for all microvascular complications of T2DM subjects (including retinopathy, neuropathy and nephropathy) analyzing 135 subjects but only for a life span between 35 and 60 years of patient age[14].

In addition, when comparing 300 T2DM subjects and 300 controls, a study by Kodiatte et al. showed that MPV levels were elevated in T2DM patients and corresponded with the increase in glucose levels and duration of T2DM[15].

As for MPV in KD, an increased MPV value in a study by Ju et al was consistent with the results of our study, but they did not compare T2DM subjects exclusively, and the MPV value corresponded with the decrease in eGFR value in subjects with chronic kidney disease (CKD)[16].

Besides the aforementioned studies, several studies have shown that platelet indices can significantly predict worsening kidney function in T2DM. Buch et al. investigated the relationship between MPV and PDW and kidney dysfunction in 300 T2DM subjects[17]. The results showed a a statistically significant correlation of MPV and PDW with diabetic nephropathy (p=0.005; p=0.007), indicating that these two parameters could be valuable markers for assessing kidney function in subjects with T2DM.

Along with platelet indices, RDW (as is commonly used to diagnose anaemia) was found to be a useful biomarker in monitoring the progression of KD in T2DM subjects. Studies have shown that elevated RDW levels may be associated with deteriorated KD and a relation between RDW and creatinine regardless of their disease, providing a conclusion that lower estimated GFR strongly predicted higher RDW values without relation to biological age or sex or haematological indices[18]. A possible explanation for this phenomenon is that RDW may reflect inflammatory processes in the body, which are common in T2DM subjects. Although that process can cause kidney damage due to the fact that Endothelial progenitor cells (EPC), being marked by the presence of CD34 receptor on their cell surface, are decreased in diseases such as T2DM and chronic kidney disease because of the endothelial damage (as it was proved that these cells play one of the crucial roles in a healing process of damaged blood vessel endothelium)[19]. Moreover, there is a relation between the EPC value and the RDW level, where the EPC value is indirectly related to the RDW value[20].

In the study conducted by Zhang et al., subjects diagnosed with both T2DM and KD were included, and their RDW levels and the progression of kidney dysfunction were monitored[21]. RDW levels were found to have a negative correlation with eGFR but a positive association with proteinuria. Moreover, the results indicated that subjects with elevated RDW levels at the beginning of the study faced a higher risk of kidney disease progression during the follow-up period. Additionally, an increase in RDW during the follow-up period was linked to the progression of kidney disease in T2DM subjects.

As a result of a study by Assulyn et al. on the RDW value in T2DM, their finding was similar to our result regarding RDW and the eGFR decline in KD but with a significant difference in KD assessment methods[22]. They analyzed RDW as a predictor of microalbuminuria presence (which could serve as an early sign of KD in T2DM) using an albumin-creatinine ratio from the urine as a

screening test for microalbuminuria excluding eGFR calculation, which resulted that RDW has a specificity of 76% and sensitivity of 37.9% for KD in T2DM subjects.

A comparison can be made with a study conducted by Kurtul et al. to assess the potential role of RDW in evaluating kidney function deterioration using serum creatinine, specifically in relation to a percutaneous coronary intervention procedure[23]. This study focused on contrast-induced nephropathy (CIN) and its association with RDW values. Their finding was that RDW carries a sensitivity of 72% and specificity of 69% for the CIN development regarding the serum creatinine increase according to the criteria mentioned above.

Regarding the complex pathogenesis of KD in subjects with T2DM, it is highly needed to direct further research towards test discoveries that may predict this complication in the development of T2DM but although potential complications that T2DM subjects will develop. T2DM subjects usually have a standard stem regarding KD – inflammation accompanied by an activated transcription factor NF kappa beta (NFkb) and hyperglycaemia. However, regardless of cause, nephrology patients have the most problems regarding inflammation and its mechanism. The NFkb mechanism is related to podocyte injury via reactive oxygen species (ROS) continuing to damage the glomerular basement membrane (due to thickening or damaging components of its structure), and that mechanism is basically initiated by hyperglycemia[24].

Additionally, hyperglycaemia is a cause of platelet aggregation, which leads to a high value of the platelet-activating factor (PAF), making a predisposition to a thrombotic state[25]. Platelet changes happen even during the preclinical sign of T2DM when hyperinsulinemia occurs due to a loss of insulin efficacy in suppressing the P2Y12 pathway, further leading to its elevation and providing platelets an additional tool for aggregation[26].

Moreover, the mechanism mentioned above is present in vascular damage related to the endothelium of kidney structure, and all those inflammatory processes are mostly regarded as chronic and low-grade inflammation, which are capable of interfering with blood cells but commonly act as undetectable regarding a diagnosis of inflammation using standard inflammatory markers such as CRP. CRP is used in clinical practice as one of the most common inflammatory markers. Friedman et al. found out that CRP cannot be used as a marker related to KD beyond already known traditional risk factors, analyzing in their study 1560 participants[27]. CRP is usually compared to microalbuminuria in the KD studies. Additionally, CRP is highly influenced by obesity, as seen in a case of metabolic syndrome further corresponding with the development of microalbuminuria and a potential kidney function loss before T2DM appearance and progression[28]. Contrary to the CRP as a gross inflammatory marker and widespread availability, high-sensitivity CRP (hs-CRP) is a high-cost inflammatory marker but a reliable marker of the KD appearance and its progression, whose levels correspond to the severity level of diabetic kidney complications[29].

In interpreting the current study's findings, several limitations should be acknowledged. Firstly, the sample size was relatively small – exclusion criteria limited the number of cases. Secondly, the study's cross-sectional design prevents us from deducing causal relations between our findings. Thirdly, by searching the literature, we could find only partial results to compare with our results – most studies were focused exclusively on RDW or platelet indices.

CONCLUSION

In conclusion, a connection between hyperglycaemia and kidney function exists in physiological and pathophysiological conditions that go both way and complex. Our study helped us in providing information about the use CBC instead of the most common inflammatory markers to predict the KD prognosis in T2DM subjects. Along with RDW and platelet indices being cost-effective, the easily calculable markers mentioned above were determined as having a practical predictive value in subjects with T2DM. The decline in kidney function is the most significant risk factor for recurrent morbidity and mortality. This information may help us reduce the number of nephropathy cases previously diagnosed with T2DM. RDW, MPV, and PDW are easily accessible, cheap, and widespread biomarkers independently related to the recognition of possible futu-

re complications, such as deterioration of kidney function in T2DM subjects.

Conflicts of Interest: Authors declare no conflicts of interest.

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2013;36:67–74.
2. Buch A, Kaur S, Nair R, Jain A. Platelet volume indices as predictive biomarkers for diabetic complications in Type 2 diabetic patients. J Lab Physicians 2017;9:84–8.
3. Matoba K, Takeda Y, Nagai Y, Kawanami D, Utsunomiya K, Nishimura R. Unraveling the Role of Inflammation in the Pathogenesis of Diabetic Kidney Disease. Int J Mol Sci 2019; 10;20:3393.
4. Charlton A, Garzarella J, Jandeleit-Dahm KAM, Jha JC. Oxidative Stress and Inflammation in Renal and Cardiovascular Complications of Diabetes. Biology (Basel) 2020;30;10:18.
5. Lee C, Park KH, Joo YS, Nam KH, Chang TI, Kang EW et al. Low High-Sensitivity C-Reactive Protein Level in Korean Patients With Chronic Kidney Disease and Its Predictive Significance for Cardiovascular Events, Mortality, and Adverse Kidney Outcomes: Results From KNOW-CKD. J Am Heart Assoc 2020;9:017980.
6. Knychala MA, Garrote-Filho M da S, Batista da Silva B, Neves de Oliveira S, Yasminy Luz S, Marques Rodrigues MO et al. Red cell distribution width and erythrocyte osmotic stability in type 2 diabetes mellitus. J Cellular Molecular Medi 2021;25:2505–16.
7. Roumeliotis S, Stamou A, Roumeliotis A, Theodoridis M, Leivaditis K, Panagoutsos S et al. Red Blood Cell Distribution Width Is Associated with Deterioration of Renal Function and Cardiovascular Morbidity and Mortality in Patients with Diabetic Kidney Disease. Life (Basel) 2020;10:301.
8. Gu L, Xue S. The Association Between Red Blood Cell Distribution Width and the Severity of Diabetic Chronic Kidney Disease. Int J Gen Med 2021;14:8355–8363.
9. Rhee J, Kwon JM, Han SH, Kim SH, Park CH, Jeon JH et al. Cockcroft-Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration equations for estimating glomerular filtration rates in cancer patients receiving cisplatin-based chemotherapy. Kidney Res Clin Pract 2017;36:342–348.
10. Bramlage P, Lanzinger S, Hess E, Fahrner S, Heyer CHJ, Friebe M et al. Renal function deterioration in adult patients with type-2 diabetes. BMC Nephrol 2020;21:312.
11. Ilhan O, Bor M. Platelet mass index and prediction of severity of transient tachypnea of the newborn. Pediatr Int 2019;61:697–705.
12. Chen B, Ye B, Zhang J, Ying L, Chen Y. RDW to platelet ratio: a novel noninvasive index for predicting hepatic fibrosis and cirrhosis in chronic hepatitis B. PLoS One 2013;8:68780.
13. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289:3273–7.
14. Mi AE, Abdallah N, Eldars W. Mean Platelet Volume and Platelet Distribution Width Correlate with Microvascular Complications in Egyptian People with Type 2 Diabetes Mellitus. Curr Diabetes Rev 2021;17:080621193947.
15. Kodiatte TA, Manikyam UK, Rao SB, Jagadish TM, Reddy M, Lingaiah HK et al. Mean platelet volume in Type 2 diabetes mellitus. J Lab Physicians 2012;4:5–9.
16. Ju HY, Kim JK, Hur SM, Woo SA, Park KA, Park MY et al. Could mean platelet volume to be a promising biomarker of progression of chronic kidney disease? Platelets 2015;26:143–7.
17. Buch A, Kaur S, Nair R, Jain A. Platelet volume indices as predictive biomarkers for diabetic complications in Type 2 diabetic patients. J Lab Physicians 2017;9:84–88.
18. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relationship between red blood cell distribution width and kidney function tests in a large cohort of unselected outpatients. Scand J Clin Lab Invest 2008;68: 745–8.
19. Nandula SR, Kundu N, Awal HB, Brichacek B, Fakhri M, Aimalla N et al. Role of Canagliflozin on function of CD34+ve endothelial progenitor cells (EPC) in patients with type 2 diabetes. Cardiovasc Diabetol 2021;20:44.
20. Rodríguez-Carrio J, Alperi-López M, López P, Alonso-Castro S, Carro-Esteban SR, Ballina-García FJ et al. Red cell distribution width is associated with endothelial progenitor cell depletion and vascular-related mediators in rheumatoid arthritis. Atherosclerosis 2015;240:131–6.
21. Zhang J, Zhang R, Wang Y, Li H, Han Q, Wu Y et al. The association between the red cell distribution width and diabetic nephropathy in patients with type-2 diabetes mellitus. Ren Fail 2018;40:590–596.
22. Assulyn T, Khamisy-Farah R, Nseir W, Bashkin A, Farah R. Neutrophil-to-lymphocyte ratio and red blood cell distribution width as predictors of microalbuminuria in type 2 diabetes. J Clin Lab Anal 2020;34:23259.
23. Kurtul A, Yarlioglues M, Murat SN, Demircelik MB, Acikgoz SK, Ergun G et al. Red cell distribution width predicts contrast-induced nephropathy in patients undergoing percutaneous coronary intervention for acute coronary syndrome. Angiology 2015;66:433–40.
24. Barutta F, Bellini S, Gruden G. Mechanisms of podocyte injury and implications for diabetic nephropathy. Clin Sci (Lond) 2022;136:493–520.
25. Shukla SD, Paul A, Klachko DM. Hypersensitivity of diabetic human platelets to platelet activating factor. Thromb Res 1992;66:239–46.
26. Angiolillo DJ, Bernardo E, Ramírez C, Costa MA, Sabaté M, Jimenez-Quevedo P et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. J Am Coll Cardiol 2006;48:298–304.
27. Friedman AN, Hunsicker LG, Selhub J, Bostom AG; Collaborative Study Group. C-reactive protein as a predictor of total arteriosclerotic outcomes in type 2 diabetic nephropathy. Kidney Int 2005;68:773–8.
28. Kahn SE, Zinman B, Haffner SM, O'Neill MC, Kravitz BG, Yu D et al. Obesity is a major determinant of the association of C-reactive protein levels and the metabolic syndrome in type 2 diabetes. Diabetes 2006;55:2357–64.
29. Tang M, Cao H, Wei XH, Zhen Q, Liu F, Wang YF et al. Association Between High-Sensitivity C-Reactive Protein and Diabetic Kidney Disease in Patients With Type 2 Diabetes Mellitus. Front Endocrinol (Lausanne) 2022;13: 885516.