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CORRELATION OF HbA1c LEVELS AND PLATELET INDICES (MPV, PDW, P-LCR, PCT) IN TYPE 2 DIABETES MELLITUS PATIENTS

Korelasi Kadar HbA1c dengan Indeks Trombosit (MPV, PDW, P-LCR, dan PCT) pada Pasien Diabetes Melitus Tipe 2

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ABSTRAK

Diabetes melitus yang berlangsung lama dapat menyebabkan komplikasi mikrovaskuler maupun makrovaskuler. Peningkatan komplikasi erat kaitannya dengan tidak terkontrolnya gula darah yang salah satunya dapat dinilai melalui parameter HbA1c. Risiko komplikasi vaskular meningkat akibat keadaan protrombotik, yang dipengaruhi oleh aktivitas trombosit. Aktivitas trombosit dapat dievaluasi melalui indeks trombosit yaitu Mean Platelet Volume (MPV), Platelet Distribution Widht (PDW), Platelet Large Cell Ratio (P-LCR) dan Plateletcrit (PCT). Penelitian ini bertujuan untuk menganalisis hubungan antara kadar HbA1c dengan indeks trombosit (MPV, PDW, P-LCR, PCT) pada pasien DM Tipe 2. Jenis penelitian yang digunakan adalah survei analitik dengan pendekatan studi korelasi menggunakan data sekunder dari 107 sampel pasien DM Tipe 2 dengan kriteria inklusi: pasien DM tipe 2 dengan kadar HbA1c ≥ 6,5% dan kriteria eksklusi: pasien tidak menerima transfusi darah 3 bulan terakhir, DBD dan Anemia yang diambil di RSUD Bandung Kiwari, dipilih menggunakan teknik purposive sampling dengan besaran sampel dihitung menggunakan rumus Lemeshow. Kadar HbA1c diukur dengan metode ion-exchange HPLC. Sedangkan Indeks trombosit dihitung menggunakan alat hematologi otomatis. Analisis statistik dilakukan dengan uji korelasi Spearman. Hasil penelitian menunjukkan terdapat korelasi positif lemah antara kadar HbA1c dengan PCT (koefisien korelasi r=0.197 dan p=0.042), sedangkan tidak ditemukan hubungan signifikan antara kadar HbA1c dengan MPV, PDW dan P-LCR dengan (MPV: r = -0,041, p = 0,67; PDW: r = 0,039, p = 0,69; P-LCR: r = -0,009, p = 0,93).

***Kata kunci**: Diabetes Melitus, HbA1c, Indeks Trombosit*

ABSTRACT

Prolonged diabetes mellitus (DM) can lead to microvascular and macrovascular complications. The increased risk of complications is closely associated with uncontrolled blood glucose levels, which can be assessed using the HbA1c parameter. The elevated risk of vascular complications arises due to a prothrombotic state, partly caused by increased platelet activity. Platelet activity can be evaluated through platelet indices, namely Mean Platelet Volume (MPV), Platelet Distribution Widht (PDW), Platelet Large Cell Ratio (P-LCR) and Plateletcrit (PCT). This study aims to analyze the relationship between HbA1c levels and platelet indices (MPV, PDW, P-LCR, PCT) in Type 2 DM patients. The type of research used is an analytical survey with a correlation study approach using secondary data from 107 samples of Type 2 DM patients with inclusion criteria: type 2 DM patients with HbA1c levels ≥ 6.5% and exclusion criteria: patients have not received blood transfusions in the last 3 months, DHF and Anemia taken at Bandung Kiwari Hospital, selected using a purposive sampling technique with a sample size calculated using the Lemeshow formula. HbA1c levels were measured using the HPLC ion-exchange method. While the platelet index was calculated using an automatic hematology device. Statistical analysis was performed using the Spearman correlation test. The results showed a weak positive correlation between HbA1c levels and PCT (correlation coefficient r = 0.197 and p =

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0.042), while no significant relationship was found between HbA1c levels and MPV, PDW and P-LCR with (MPV: r = -0.041, p = 0.67; PDW: r = 0.039, p = 0.69; P-LCR: r = -0.009, p = 0.93).

Keywords: Diabetes mellitus, HbA1c, platelet indices

INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases in which hyperglycemia occurs due to abnormalities in insulin secretion, insulin function, or both.[1] Indonesia currently ranks fifth in the world for diabetes. The number of people with diabetes reached 20.4 million in 2024 and is predicted to increase to 28.6 million by 2050.[2]

Long-term diabetes can lead to various complications, categorized as microvascular and macrovascular. The most common complication in people with diabetes mellitus is cardiovascular disorders, with a prevalence reaching 39.2%.[3]The risk of vascular complications increases due to a prothrombotic state, which facilitates thrombus formation and leads to blood vessel occlusion, potentially damaging organs. One of the main factors triggering this prothrombotic state in people with diabetes is increased platelet activity. Furthermore, platelets in diabetic patients are known to be larger and tend to be more active, as platelet size is related to their aggregation capacity and the release of their granule contents.[4,5]

In some cases of diabetes mellitus, increased platelet size leads to increased platelet activity. Enlarged platelets undergo strong contractions of their contractile proteins, which trigger the release of granules containing various active substances. As a result, platelets become stickier and adhere to collagen fibers, releasing ADP and enzymes involved in the formation of thromboxane A2 into the bloodstream. This combination of ADP and thromboxane A2 promotes platelet aggregation, ultimately forming a platelet plug.[6] Platelets have several indices consisting of Mean Platelet Volume (MPV), an increase in MPV indicates an increase in platelet diameter that can be used as a marker of platelet production and activation rate. Platelet Distribution Width (PDW), is an indicator of volume variability in platelet size and increases with platelet anisocytosis, Platelet Large Cell Ratio (P-LCR), is an indicator of larger platelet circulation (> 12 fL), which is reported in percent (%) and Plateletcrit (PCT), PCT is the volume occupied by platelets in the blood as a percentage. Platelet indices are indicators of platelet activity, and their values can be determined by examination on a Hematology Analyzer.[7]

The occurrence of complications in DM, both microvascular and macrovascular, as well as death, is closely related to uncontrolled blood sugar.[8] Glucose monitoring is key to achieving glycemic targets. The HbA1c test is a more reliable way to objectively monitor blood glucose levels.[1] Research data shows that every 1% decrease in HbA1C values can reduce 21% of DM-related deaths, 14% of myocardial infarctions, and 37% of microvascular complications.[8]

Based on research conducted by Katarina Noviyanti in 2022, it was shown that there was a moderate positive relationship between HbA1c levels and MPV platelet index values (r=0.43; p=<0.05) with an average of 10.10 ± 0.85 fL and the highest value of 12.4 fL, and HbA1c and PDW also had a positive relationship (r=0.48; p=<0.05) with an average of 11.61 ± 1.65 fL and the highest value of 17.1 fL.[1]A literature study conducted by Mahdalena in 2023 concluded that glycemic control can reduce platelet hyperactivity, thus playing a role in preventing or delaying the occurrence of vascular complications due to diabetes.[9]HbA1c and platelet index are tests that can be used to see the progression of diabetes

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mellitus so that complications can be prevented. In other words, there is a relationship between glycemic control and several platelet index values.[9] To evaluate the existence of this relationship, the author is interested in conducting research on the Correlation of HbA1c Levels with Platelet Indices (MPV, PDW, P-LCR, and PCT) in Type-2 DM Patients.

The purpose of this study was to analyze the relationship between HbA1C levels and MPV values in Type-2 DM patients, to analyze the relationship between HbA1C levels and PDW values in Type-2 DM patients, to analyze the relationship between HbA1C levels and P-LCR values in Type-2 DM patients, and to analyze the relationship between HbA1C levels and PCT values in Type-2 DM patients.

METHODS

The type of research used was an analytical survey with a correlation study approach because the researchers wanted to determine the relationship between the research variables. This study used secondary data obtained from the Bandung Kiwari Regional Hospital Laboratory.

This study was conducted from January to October 2024 at the Bandung Kiwari Regional General Hospital. The population was patients with type 2 diabetes mellitus (DM). The sample consisted of patients who underwent HbA1c and Cell Blood Count (CBC) tests at the Bandung Kiwari Regional General Hospital between January and October 2024.

The inclusion criteria in this study were Type 2 DM patients with HbA1C levels ≥ 6.5%, while the exclusion criteria in this study were patients receiving blood transfusions in the last 3 months, patients diagnosed with Dengue Hemorrhagic Fever (DHF), and Anemia.[1]

This study used a purposive sampling technique, where subjects were selected intentionally based on certain characteristics that aligned with the research objectives. The sample size was calculated using the Lemeshow formula, and the results showed that the minimum required sample size was 96 individuals. To anticipate the possibility of data loss (dropout) of 10%, the sample size was then increased to a minimum of 107 individuals. The data used in this study were secondary data obtained from HbA1c and platelet index examination records of patients at Bandung Kiwari Regional Hospital.

The data processing was carried out through coding, data entry, and editing stages, and then processed using the S PSS version 30 program. Data analysis included descriptive analysis and hypot hesis testing. Univariate analysis was p erformed on each variable to determine the characteristics of the variables. The independent variable in this study was t he HbA1c level, and the dependent vari able was the platelet index value (MPV, PDW, P-LCR, PCT). Normal Platelet In dex values are MPV: 7.2-11.7 fl; PDW: 8.3-56.6% (9.0-13.0 fL); P-LCR: 15–35; PCT: 0.22–0.24%. The research instru ment used secondary data from the res ults of HbA1c level examinations, exami ned using a High Performance Liquid C hromatography (HPLC) tool, and platele t index values were examined using a H ematology Analyzer. The research data were subjected to statistical tests using SPSS v30. Bivariate analysis was perfo rmed to determine the relationship betw een HbA1c, MPV, PDW, P-LCR, and P CT in patients with type 2 diabetes. Dat a for each variable were tested using th e Kolmogorov-Smirnov test to determin e normality. If the data were normally di stributed, a Pearson correlation test wa s performed, while if the data were not normally distributed, a Spearman correl ation test was performed.

RESULT

This study was conducted at Bandung Kiwari Regional Hospital in October 2024. Data were collected on HbA1c and platelet indices (MPV, PDW, P-LCR, and PCT) from patients

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diagnosed with type 2 diabetes between January and October 2024.

Table 1. Frequency of Gender and Age of Type 2 DM Patients

Variables	n	%
Gender		
Man	51	47.7
Woman	56	53.3
Age		
<30	3	2.8
31-40	7	6.5
41-50	14	13.1
51-60	34	31.8
61-70	35	32.7
71-80	14	13.1
Total	107	100.0

Table 1 shows the distribution and frequency of gender and age of Type 2 DM patients, namely there is a slight difference between the number of men 51 people (47.7%) and women 56 people (52.3%), in this study. It can be seen that the majority of participants are aged between 51-70 years, with a proportion of 64.5% (34 participants aged 51-60 years and 35 participants aged 61-70 years).

Table 2. Descriptive Statistical Data of Research Subjects

Variables (n=107)	Mean ± SD	Median (Min-Max)
Age	58.30±12.01	(28-79)
HbA1c	10.43±2.85	10.00 (6.6-18.7)
Variables (n=107)	Mean ± SD	Median (Min-Max)
MPV	9.629±0.85	9,500 (7.9-12.1)
PDW	10.48±1.56	10,200 (7.8-15.3)
P-LCR	22,012±6.40	21,400 (9.4-39.3)
PCT	0.3034±0.96	0.2900 (0.15-0.4)

Table 2 shows the results of descriptive statistics obtained the average HbA1c of Type 2 DM patients is 10.43 with a standard deviation of 2.86 (Min-Max: 6.6-18.7), indicating a fairly large variation. The average MPV is 9.63 with a standard deviation of 0.85 (Min-Max: 7.9-12.1), which indicates that although there is variation, this value is still within the acceptable range. Meanwhile, for PDW shows an average of 10.48 with a standard deviation of 1.56 (Min-Max: 7.8-15.3), P-LCR has an average of 22.01 with a standard deviation of 6.40 (Min-Max: 9.4-39.3) and PCT has an average of 0.30 with a standard deviation of 0.096 (Min-Max: 0.15-0.74)

Table 3. Results of Normality Test Using Kolmogorov-Smirnov

Variables	N	p	Data Normality
HbA1c	107	0.020	Abnormal
MPV	107	0.053	Normal
PDW	107	0.006	Abnormal
PLCR	107	0.128	Normal
PCT	107	0.007	Abnormal

The results of the normality test using Kolmogorov-Smirnov showed that several variables, such as HbA1c (p=0.02), PDW (p=0.006), and PCT (p=0.007) were not normally distributed (p<0.05) as seen in Table 3. Data is said to be normally distributed if the significance value is p>0.05. In Table 3 it can be seen that of the 5 variables, the data that is normally distributed is only MPV with a significance value of p=0.053.

The correlation test used in this study was the Spearman test because the data were not normally distributed. The Spearman correlation test results showed no significant relationship between HbA1c and MPV (p=0.67, r=-0.041). The correlation test conducted on the PDW parameter also showed no correlation (p=0.69, r=0.039), and the P-LCR parameter (p=0.93, r=-0.009) also showed no correlation. Meanwhile, there was a weak positive correlation between HbA1c and PCT with a correlation coefficient of 0.197 and a 2-tailed sig. 0.042 (p<0.05).

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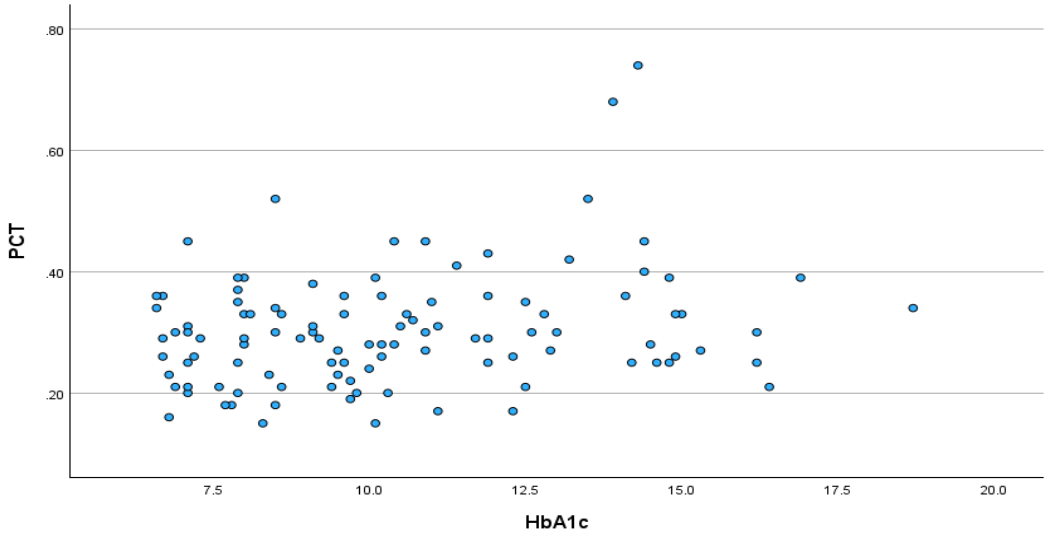

Figure 1. Scatter Plot Graph of the Relationship between HbA1c Levels and PCT

Figure 1 is a scatter plot showing the relationship between HbA1c levels and PCT. Based on the correlation test, there is a weak positive correlation between HbA1c levels and PCT, so if a line is drawn on the scatter plot, the results are less than linear.

DISCUSSION

This study involved 107 subjects who met the inclusion and exclusion criteria. Fifty-one (47.7%) of the subjects were male, and 56 (53.3%) were female. The prevalence of type 2 diabetes is higher in women than in men. Women over the age of 40 have several risk factors, one of which is premenopause, which leads to a decrease in estrogen synthesis.[10.11]

In menopausal women, the hormones estrogen and progesterone affect the response of body cells to insulin. If their levels decrease, the body's ability to respond to insulin will also decrease. This is thought to be one of the factors that increases the incidence of Type 2 DM in women [12]

The subjects in this study were aged 28 to 79 years, with an average age of 58.30 ± 12.01 years. The results showed that the majority of participants were over 30 years old. This is because diabetes sufferers under 30 years old are generally classified as type 1 diabetes mellitus or Maturity Onset Diabetes of the Young (MODY), which is not included in this study's criteria. Age itself is one of the main risk factors for diabetes mellitus. Ilunga Tshiswaka in his research revealed that the prevalence of diabetes mellitus tends to increase significantly after the age of 45 years.[13]

At Sanjiwani Gianyar Regional Hospital, the majority of type 2 DM patients are aged between 61 and 80 years (50.9%), and around 67% of diabetes cases are experienced by the elderly aged over 65 years.[14] Insulin sensitivity decreases with aging. The aging process also contributes to decreased insulin sensitivity, with insulin secretion decreasing by approximately 0.7% per year, and in individuals with impaired glucose tolerance, this decline can double.[15] The risk of developing diabetes mellitus increases with age, especially in the elderly. As we age, our immune system and physical strength decline, making us more susceptible to unhealthy lifestyle choices and the development of various diseases, including diabetes.[16] Furthermore, the risk of diabetes increases significantly after age 45 and increases sharply after age 65 due to decreased physical activity, weight gain, and loss of muscle mass. These conditions can lead to pancreatic dysfunction, which ultimately reduces insulin production and increases blood glucose levels.[17]

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The average HbA1c level in the study subjects was 10.43±2.855. The results showed that the lowest HbA1c level was 6.6% and the highest was 18.7%. In this study, 26.2% of the subjects had HbA1c levels <8% and 73.8% had HbA1c levels >8%. According to the 2021 Type 2 Diabetes Mellitus Consensus, diabetes mellitus control.

HbA1c levels are considered good if they are below 6.5%, moderate if they are between 6.5% and 8%, and poor or uncontrolled if they exceed 8%. Poorly controlled diabetes mellitus can lead to various complications related to the disease.[17]

Based on the results of the hypothesis test analysis using the Spearman correlation test between Hba1c and MPV, the sig. (2-tailed) value is 0.675, and the correlation coefficient is -0.041. This indicates that there is no correlation between HbA1c levels and MPV values in type 2 DM patients, in line with research conducted by Muhammad Sahid in 2023 regarding the relationship between HbA1c and MPV in type 2 diabetes mellitus patients. The study showed that there was no relationship between HbA1c and MPV values , with a p value of 0.100, this is also in line with research conducted by Astuti et al in 2014 with a p value of 0.907.[7.17]

The mean PDW value in this study was 10.48±1.5583, with the lowest value being 7.8 and the highest being 15.3 fL. The results of the Spearman correlation test between HbA1c levels and PDW values showed no significant relationship, indicating that an increase in HbA1c was not in line with an increase in PDW values. This is similar to a study conducted by Kshirsagar RM et.al., which stated that in type 2 DM patients compared to controls, HbA1c did not have a significant relationship with platelet indices, either MPV or PDW.[18]

In contrast to research conducted by Buch et.al.[19], in 2017, which showed a positive relationship between HbA1c and platelet index. Likewise, research conducted by Shilpi et.al., stated that the platelet index of type 2 DM sufferers with HbA1c levels ≥ 6.5% was significantly higher than that of type 2 DM sufferers with HbA1c levels < 6.5%.[20]Furthermore, research conducted by Noviyanti in 2022 also found a significant relationship between HbA1c and MPV and PDW.[1]

The difference in the results of this study with previous studies may be due to differences in the number of samples, the sample criteria used were that the research subjects did not consume antiplatelet drugs such as clopidogrel, while in this study no assessment was carried out on that so it is possible that subjects who had experienced complications in this study such as polyneuropathy, stroke and cardiovascular were given antiplatelet drugs that can inhibit the blood clotting process, thus causing there to be no relationship between HbA1c levels and platelet index.

The P-LCR value in this study was 22,012±6.4042, with the highest value of 39.3% and the lowest of 9.4%. The results of the correlation test between HbA1c and P-LCR showed no significant correlation, meaning that the increase in HbA1c levels was not related to the P-LCR value. This study is consistent with a study conducted by Ramdhani and colleagues in 2013, which showed no significant difference in platelet indices (MPV, PDW, and P-LCR) between type 2 DM patients with microvascular complications and those without complications.[21]

To date, researchers have not found any other studies specifically examining the relationship between HbA1c levels and the platelet index P-LCR. Platelet Large Cell Ratio (P-LCR) is the percentage of platelets larger than 12 fL out of a normal platelet count. The normal range for P-LCR is 10–30%. P-LCR has an inverse relationship with platelet count but is positively correlated with MPV and PDW. When platelet function is impaired, the risk of

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bleeding can increase.[22] In this study, the average P-LCR value was still within normal limits, namely 22.01%, although there were several samples with high values, with a maximum value reaching 39.3%.

The PCT value in this study had an average of 0.3034±0.9628% with the highest value of 0.74% and the lowest of 0.15%. The results of the Spearman correlation test between HbA1c levels and PCT values showed a weak positive correlation with a correlation coefficient value of 0.197 and a 2-tailed sig. of 0.042 ($p<0.05$). Researchers have not found any previous research regarding the relationship between HbA1c levels and PCT values. Plateletcrit is the same as hematocrit in erythrocytes, PCT values are influenced by the number of platelets.[22] This study found 18.69% of subjects with PCT values below the normal range, 4.67% within the normal range, and 76.64% above the normal range. The study also found 73.8% of subjects with HbA1c values >8%, an indicator of uncontrolled diabetes, with 78% experiencing an increase in PCT values.

The normal value for PCT parameters is 0.22%-0.24%.[23.24] Unlike other platelet indices, PCT has a weak positive relationship with HbA1c. This is likely because comorbid conditions or medications received by the subject can affect the relationship between HbA1c and other platelet indices, but not PCT in the same way. PCT is more reflective of total platelet count than platelet function or size.

In people with diabetes mellitus, platelet function changes occur, with increased platelet activity compared to individuals without diabetes. Platelets in DM patients exhibit higher expression of P-Selectin and GP IIb/IIIa receptors, making them more responsive to agonist stimuli than platelets in non-diabetic individuals. This is related to disruptions in the platelet signaling pathway, leading to increased platelet activation and aggregation, known as platelet hyperreactivity. This condition is characterized by increased thromboxane A2 production.[21]

Larger platelets tend to be more reactive and prone to aggregation because they contain more granules, release greater amounts of serotonin and thromboglobulin, and produce more thromboxane A2 than smaller platelets. This contributes to their procoagulant effects and increases the risk of thrombotic vascular complications. Therefore, a relationship is suspected between platelet function and activation, as reflected in Mean Platelet Volume (MPV), and the development of vascular complications; an increase in MPV is thought to reflect a thrombogenic process. Furthermore, mild bleeding can occur due to rupture of atherothrombotic plaques, which then increases platelet consumption, amplifies hyperreactivity, and stimulates platelet production in the bone marrow.[21]

The platelet index is a marker of platelet activity or function and thrombopoiesis in the bone marrow. Platelet activity in type 2 diabetes mellitus is influenced not only by hyperglycemia and insulin resistance but also by dyslipidemia, inflammation, and the presence of comorbidities. Dyslipidemia can affect platelet function and increase the risk of blood clots.

Platelet activity in diabetes mellitus will increase the MPV value more if accompanied by comorbidities compared to hyperglycemia alone.[17] Some examples of comorbidities that can affect platelet activity include coronary heart disease, hypertension, chronic kidney disease, liver disease, infections, cancer, autoimmune diseases, and obesity. Some of these diseases can affect platelet activity. Therefore, although hyperglycemia is an important factor in increasing platelet activity, it cannot be the sole cause. Instead, a complex interaction between various metabolic and physiological factors contributes to

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increased platelet activity in patients with diabetes mellitus.

This study did not assess random glucose levels. HbA1c levels tend to be stable for three months in DM patients, while platelet lifespan is only 7-10 days. Therefore, it is possible that the two parameters are not directly related due to differences in the duration of the physiological parameters measured. HbA1c reflects long-term glycemia, while platelet indices tend to fluctuate more in the short term, making it difficult to correlate HbA1c and platelet indices data.

Directly, without considering other factors such as diabetes duration, glycemic control, or the presence of vascular complications, acute glycemic changes may have a greater impact on platelet indices than on HbA1c, which is more stable over the long term. Differences in the lifespan of erythrocytes and platelets, as well as different mechanisms, make the direct relationship between HbA1c and platelet indices in DM patients small or even non-existent. A relationship may only occur under specific conditions that affect both parameters simultaneously. Furthermore, the use of antiplatelet drugs must be considered because antiplatelet drugs, commonly prescribed to type 2 DM patients with cardiovascular complications or stroke, inhibit thromboxane A2, thus inhibiting thrombus formation. Therefore, this may have influenced the results of this study.

The advantage of this study compared to previous studies is that it assessed the PCT platelet index in relation to HbA1c levels. The limitation of this study is that it only used secondary data from the results of HbA1c level and platelet index examinations without assessing the consumption of anti-platelet drugs in the research objects, which may provide different results regarding the relationship between HbA1c levels and platelet index in Type 2 DM patients.

CONCLUSION

There is no significant relationship between HbA1c levels and MPV values in Type-2 DM patients, there is no significant relationship between HbA1c levels and PDW values in Type-2 DM patients, there is no significant relationship between HbA1c levels and P-LCR values in Type-2 DM patients, there is a relationship between HbA1c levels and PCT values in Type-2 DM patients with a weak positive correlation.

Suggestions for hospital institutions are to integrate PCT monitoring as part of diabetes management, especially for patients with high HbA1c levels (>8%) and for further research to conduct research with a larger and more comprehensive sample size to explore the mechanisms underlying the relationship between HbA1c and Platelet Index, also including other variables that influence this relationship such as random glucose levels, inflammatory factors or comorbidities.

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