HEMATOLOGY IN DIABETES MELLITUS; DIAGNOSTIC AND PROGNOSTIC ROLE OF COMPLETE BLOOD COUNT AND HEMOGRAM-DERIVED NOVEL MARKERS IN DIABETES MELLITUS AND ITS COMPLICATIONS.

ABSTRACT

Diabetes mellitus a chronic, progressive, metabolic disorder characterised by hyperglycemia initially because of tissue insulin resistance and gradually progressing to complete loss of secretory activity of the beta cells of the pancreas, most frequently caused by impaired insulin secretion, resistance to tissue actions of insulin, or a combination of both. Study of hematological changes in diabetic patients along with complete blood count(CBC), hemogram derived novel markers including Neutrophil-Lymphocyte ratio (NLR),Monocyte-Lymphocyte ratio (MLR),Red cell distribution width-Platelet ratio (RPR),Mean Platelet Volume to Lymphocyte Ratio (MPVLR) Platelet-Lymphocyte ratio (PLR) etc and its diagnostic and prognostic value in diabetes mellitus and its complications are reviewed in this literature review which may shed fresh light on developing new treatment plans on diabetic patients and help doctors in the diagnosis and prognosis of diabetic patients with or without complications, helping with diabetes early diagnosis, and early detection of long-term complications in diabetes patients, which results in improving quality of life in diabetic patients.

Keywords: Diabetes mellitus, Complete blood count, Hemogram, Anemia, Vascular Complications

1. INTRODUCTION

Diabetes mellitus can be subdivided in to

Type 1, which is characterised by a total lack of insulin production and is brought on by auto-immune beta-cell destruction in the pancreas,

Type 2, which manifests when the body's ability to manufacture enough insulin to overcome resistance increases abnormally,

Type 3. gestational diabetes, a type of glucose intolerance that affects some pregnant women;

Type 4. a set of additional types of diabetes caused by particular genetic disorders of beta-cell activity or insulin action, diseases of the pancreas, or medicines or chemicals [1]

“Diabetes mellitus is a metabolic disorder that is chronic, progressive, and largely characterised by hyperglycemia. The pathophysiology of type II diabetes mellitus, a spectrum of diseases initially caused by tissue insulin resistance and gradually progressing to a state characterised by complete loss of secretory activity of the beta cells of the pancreas, is thought to be most frequently caused by impaired insulin secretion, resistance to tissue actions of insulin, or a combination of both” [2] [3].

1.1 Pathophysiology of Diabetes mellitus

“One of the most prevalent metabolic disorders, Type 2 Diabetes mellitus (T2DM), is brought on by a confluence of two major factors: impaired insulin production by pancreatic beta cells and impaired insulin sensitivity in target tissues. The molecular mechanisms involved in the synthesis, release, and detection of insulin are closely regulated because these actions are critical for maintaining glucose homeostasis. A metabolic imbalance that is responsible for the development of the disease might be caused by flaws in any of the mechanisms involved in these processes. To prevent, control, treat, or reverse the pathophysiology of T2DM and its problems, it is essential to understand the mechanisms involved in each stage of the development and complications of T2DM” [4]. “Several studies have revealed that an important factor in the onset of complications brought on by hyperglycemia is the excessive creation of extremely reactive oxygen and nitrogen species. Excess production and/or insufficient removal of these reactive species results in vascular dysfunction, damage to cellular

proteins, membrane lipids, and nucleic acids" [5]. "The macrovascular problems include heart disease, stroke, and peripheral artery disease, while the microvascular complications are neuropathy, nephropathy, and retinopathy" [6].

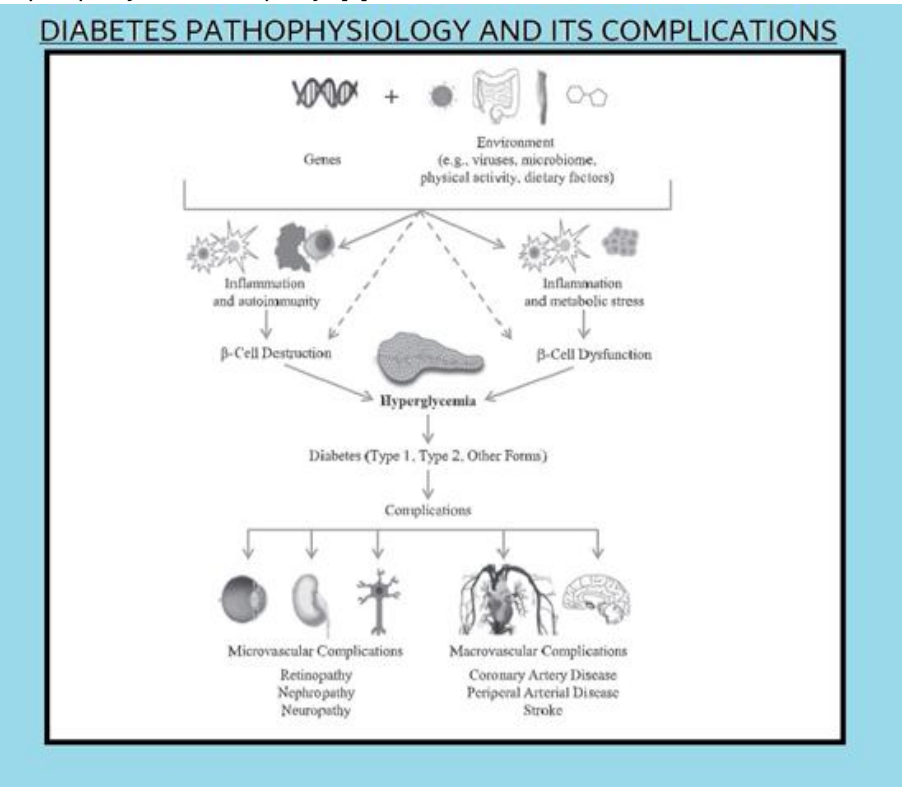

Fig. 1. Diabetic pathophysiology and its complications. [7]

Multiple comorbidities are common in type 2 diabetes (T2DM) patients, and these comorbidities may impact the selection of antihyperglycemic medications. The most prevalent comorbid conditions include hypertension, obesity, hyperlipidemia, cardiovascular disease, and chronic renal disease [8].

Anemia frequently coexists with diabetes mellitus. Many research studies point out various additional factors which may contribute to anemia in diabetic patient which includes.

1. Oxidative stress (reduced glutathione) has a strong and significant impact on the levels of glutathione peroxidase and glutathione reductase, which may lower haemoglobin concentration in diabetic patients
2. Increased erythrocyte mechanical fragility in diabetes mellitus

3. Diabetes patients who are using hypoglycemic agents, including metformin for a longer period, have a higher risk of vitamin B12 deficiency, resulting in anemia

4. Relative erythropoietin (EPO) deficiency

5. Anemia in people with diabetes mellitus (DM) is frequently correlated with chronic disease-related anaemia brought on by inflammatory conditions or issues with iron metabolism. Hepcidin can prevent the intestines from absorbing iron, which lowers the serum iron levels.
6.Hemolytic anemia because of medication, including metformin.
7. Shortened erythrocyte lifetime by the coexistence of micro and macro angiopathies with hyperglycemia
8. Effects of hyperglycemia on red blood cells (RBC), including glycation of haemoglobin, reduced deformability, and shortened lifespan.

Chronic low-grade inflammation is linked to type 2 diabetes mellitus. According to some studies, even when it is within the normal range, an elevated leukocyte count can predict the onset of micro and macro vascular issues in type 2 diabetes patients.

Diabetes patients are more likely to experience vascular complications and have altered platelet morphology and functions, which may suggest that this population has more reactive and

aggregatable platelets. The early diagnosis of long-term complications in diabetic patients may be aided by a knowledge of platelet morphology in this condition.

Many of the hemogram indices including Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) ,Red cell distribution width(RDW) , mean platelet volume (MPV), platelet distribution width(PDW), plateletcrit (PCT), P-LCR (platelet larger cell ratio) could be helpful tools in monitoring diabetes mellitus and can be used as potential markers of its complications. Haematological indices are simple, affordable, valuable, and easily available laboratory parameters, which help medical practitioners who are the first line of care for diabetes patients who can use these indicators in everyday practice for diagnosis and follow-up.

According to some of the latest studies, along with these hemogram indices, hemogram derived novel markers, including

- Neutrophil-Lymphocyte ratio (NLR)
- Monocyte-Lymphocyte ratio (MLR)
- Red cell distribution width-Platelet ratio (RPR)
- Mean Platelet Volume to Lymphocyte Ratio (MPVLR)
- Platelet-Lymphocyte ratio (PLR) can be used as predictive and prognostic markers in diabetes and its complications.

2. Objective of the Study

The main objective of the review article includes a review of various research scholarly articles published on hematological changes happening in patients with diabetes mellitus and reviewing of various articles on using complete blood count and hemogram-derived novel markers in the diagnosis and prognosis of diabetes mellitus and its complications. These findings may help doctors in the diagnosis and prognosis of diabetic patients with or without complications which aids in the early diagnosis of diabetes, and may be helpful in the early detection of long-term complications in diabetes patients, which results in improvement of the diabetic patient's quality of life.

3. Methodology

The proposed study reviews the relevant literature using the method of data collection. The information needed for the study was gathered from secondary sources, including journals, magazines, research papers, and publications.

4.Result

Related scholarly work Hematology in diabetes, diagnostic and prognostic value of CBC and hemogram-derived novel markers in the diabetes mellitus and its complications.

Table 1: Relevant studies on anemia, red cell morphology, red cell indices in diabetes mellitus patients

Serial No:	AREA OF RESEARCH/ RESEARCH TITLE	FINDINGS/OUTCOMES	REFERENCE
1	Patients with type 2 diabetes exhibit increased erythrocyte mechanical fragility.	According to Giuseppe Lippi et al., the main correlate of increased erythrocyte mechanical fragility in this patient group is fasting plasma glucose, and patients with type 2 diabetes had considerably higher erythrocyte mechanical fragility than comparable nondiabetic participants.	Giuseppe Lippi et al. [2012] [9]
2	Effective of oxidative stress on human red cells	According to the findings of a study conducted by Qassim University in Saudi Arabia on the relationship between oxidative stress and the prevalence of anaemia in diabetic patients, oxidative stress (reduced glutathione) has a strong and significant impact on the levels of glutathione peroxidase and glutathione	Hisham Waggiallah et al [2011] [10]

		reductase, which may lower haemoglobin concentration in diabetic patients. This suggests that diabetics without nephropathy may develop anaemia due to the oxidative stress of diabetes mellitus.	
3	Diabetes and anemia	Anemia must be detected screened in diabetic patients together with other risk factors, and it must be managed effectively to enhance overall clinical results.	Sahay M et al [2017] [11]
4	Anemia prevalence among adult outpatients with diabetes in Northeast Ethiopia	Adults with diabetes who visited the diabetes outpatient clinic in Northeast Ethiopia, including those without renal disease, frequently had anaemia. The study emphasised the necessity of including anaemia screening in normal diabetes care to enable early anaemia detection and treatment, improving the overall care of diabetes patients.	Temesgen Fiseha et al [2019] [12]
5	The frequency of newly discovered anaemia in newly admitted diabetics	The study conducted to identify newly diagnosed anaemia in diabetes patients highlights the requirement for haematological screening in all diabetics presenting to healthcare facilities. In addition to chronic kidney disease, dietary iron and vitamin deficiency, glycemic management, the existence of CKD, retinopathy, and gastrointestinal issues need to be assessed and treated.	Nadia Shams et al. [2015] [13]
6	Relationship between anaemia and diabetes mellitus in Korean people, according to sex	The study discovered a significant link between DM and anaemia, which was more pronounced in males than in women. Compared to the non-DM group, the prevalence of anaemia was significantly greater in the DM group.	Mihye Kim et al. [2020] 14]
7	Anemia in Diabetes Mellitus Patients: Frequency and Progression	A retrospective study of 227 Saudi diabetic patients who were followed up as outpatients for a year found that 55.5% of the group had anaemia. Anemia is a frequent side effect of diabetes and can manifest early, even in the absence of renal impairment. This calls for early detection of anemia as well as additional research to determine its possible causes.	Al-Salman M [2015] [15]
8	An analysis of the incidence of type 2 diabetes patients with anemia in teaching hospitals	In this study, patients with Type II diabetes mellitus had a higher prevalence of anaemia. Anemia was more common in diabetic women than in diabetic men. According to the study's findings, anaemia is a frequent occurrence among diabetic patients with poorly managed blood sugar levels. All Type II diabetes mellitus patients should undergo routine anaemia screenings as this could aid in the early detection and management of anaemia.	Muhammed N Shabeeb et al. [2021] [16]
9	Anemia in Patients with Type 2 Diabetes Mellitus	Patients with DM2 frequently experience anaemia. The group of alterations that have been noticed defines the anaemia of chronic disease, which has an impact on diabetic patients' quality of life and is linked to comorbid conditions that considerably raise the risk of cardiovascular diseases.	Jéssica Barbieri et al. [2015] [17]

10	Anemia and its associated factors among type 2 diabetes mellitus patients	Anemia among T2DM was substantially correlated with poor glycemic control, decreased egfr, the prevalence of DM comorbidities, duration of DM >10 years, and age >60 years. All T2DM patients should undergo routine for anemia screenings to aid in the early diagnosis and treatment of anaemia.	Mitku Mammo Taderegew et al. [2020] [18]
11	Anemia and microvascular complications in patients with type 2 diabetes mellitus	Anemia is a frequent DM consequence that is linked to the severity of the disease and microvascular complications. The study also noted a considerable correlation between anaemia and neuropathy, nephropathy, and retinopathy.	Mahboobeh Sadat Hosseini et al. [2014] [19]
12	Anemia With Erythropoietin Deficiency early occurrence in Diabetic Nephropathy	Although anaemia caused by EPO insufficiency can develop early in diabetic nephropathy (DN) before the start of advanced renal failure, it seldom does so in non-diabetic renal disease of similar severity. Clarification of the pathogenesis is necessary.	, Deborah R Bosman et al. [2001] [20]
13	Patients with chronic renal disease are more likely to have anaemia when they have diabetes mellitus.	The higher ferritin levels in diabetics in this study suggest that subclinical inflammation in diabetic individuals with moderate CKD may be the most significant underlying reason for anemia. Anemia in diabetic CKD patients should be detected and treated earlier than in non-diabetic counterparts due to the considerable morbidity and mortality that anaemia is associated with.	Charalampos Loutradis et al. [2016] [21]
14	Hepcidin and anemia relationship in controlled and uncontrolled Type-2 Diabetes Mellitus	Anemia in people with diabetes mellitus (DM) is frequently correlated with chronic disease-related anaemia brought on by inflammatory conditions or issues with iron metabolism. Hepcidin can prevent the intestines from absorbing iron, which lowers the serum iron levels. Patients with Type-2 Diabetes Mellitus (T2DM) were investigated to determine the association between serum hepcidin levels and anaemia. The average haemoglobin level of the managed type 2 DM patient population is greater than the average haemoglobin level of the uncontrolled type 2 DM patient population. The mean hepcidin level was lower in the type 2 DM patients with controlled diabetes than in those with uncontrolled type 2 DM. The mean haemoglobin and hepcidin levels were significantly different between the groups of people with managed and uncontrolled T2DM patients. Additionally, in people with type 2 diabetes, there was a statistically significant relation between low hepcidin levels and anaemia.	Ni Ketut Puspa Sari et al. [2021] [22]
15	Metformin induced Vitamin B12 deficiency	In T2DM patients, continuous metformin medication raises the risk of vitamin B12 deficiency and the associated medical problems. Based on studies including 100 patients and 100 controls, 48% of the participants had vitamin B12 deficiencies. The study found that patients with T2DM who have used metformin for a longer period of time and who are taking larger dosages of metformin have a higher risk of vitamin B12	Talar M Raqib et al. [2022] [23]

		deficiency.	
16	Vitamin B12 deficiency ,deep vein thrombosis, , and hyperhomocysteinemia in a diabetic patient using metformin	Metformin use for an extended period of time may cause vitamin B12 deficiency, which could then result in hyperhomocysteinemia. So, in diabetic individuals, hyperhomocysteinemia may raise the risk of vascular thrombosis. The role of metformin in causing vitamin B12 deficiency, which may serve as an additional risk factor for venous thrombosis in diabetic patients, was strongly suggested by a case study on a 65-year-old Taiwanese diabetic woman who had been treated with metformin for 6 years and had experienced swelling of the left lower extremity for 3 months. The paper also emphasised the significance of monitoring vitamin B12 levels while on metformin.	Hsuan-Yu Lin et al. [2007] [24]
17	Metformin-induced hemolytic anemia	A 17-year-old boy was admitted to the hospital to receive treatment for acute lymphoblastic leukaemia. Without any clinical indication, hyperglycemia was identified, and metformin was given to treat the insulin resistance brought on by steroids. The patient's haemoglobin level dropped on the second day of metformin therapy, and a direct Coombs test revealed positive results for immunoglobulin G but negative results for complement. A Coombs indirect test found negative. Glucose-6-phosphate dehydrogenase was present with in normal range. Metformin was discontinued because of the possibility of medication-induced hemolytic anaemia. Red blood cell transfusions were not necessary since the jaundice eventually subsided. Although metformin adverse effects are rare, this case demonstrated that doctors should be aware of them.	, Serap Kirkiz et al. [2014] [25]
18	Effects of metformin treatment and glycemic state on oxidative stress and red blood cell parameters in type 2 diabetic patients	The purpose of the study was to evaluate the effects of metformin treatment and glycemic control on changes in red blood cell (RBC) indices and oxidative stress in type 2 diabetic individuals. Overall, the findings showed that all diabetic groups had significantly lower haemoglobin concentrations than controls, whereas red cell distribution width (RDW) values were significantly higher. The study by Abdel Moniem et al demonstrated how metformin administration reduced oxidative stress and improved glycaemic status, which were reflected in certain RBC indicators. Although glycaemic and oxidative stress status improved in all metformin-treated groups, haemoglobin concentration significantly decreased, indicating that metformin-induced anaemia is unrelated to diabetic problems. Also the study found out that Patients using metformin and insulin showed a significant decrease in their erythrocytes (rbcs) count.	Abdel Moniem et al [2019] [26]

19	Risk of anemia with metformin use in type 2 diabetes	Metformin use is related with an early risk of anaemia in people with type 2 diabetes, according to a randomised clinical trial (RCT)that examined the relationship between the two variables. This conclusion was repeated in one real-world investigation and was consistent across two clinical trials. Although the exact cause of early fall of haemoglobin is unknown, it is unlikely due to vitamin B12 deficiency alone	Louise A Donnelly et al. [2020] [27]
20	Effects of iron deficiency anaemia on haemoglobin A1C levels in people with diabetes with controlled plasma glucose control	Hba1c values rise in diabetics with controlled plasma glucose levels who have iron deficiency anaemia. Patients with plasma glucose levels between 100 and 126 mg/dl are more likely to experience an elevation. Thus, iron deficiency anaemia should be taken into account before altering the diabetic treatment plan.	Alap L. Christy et al. [2014] [28]
21	Low erythropoietin levels forecast faster renal function decline in diabetic patients with anemia:	Even in diabetic patients without chronic renal disease, relative erythropoietin (EPO) deficiency needs to be taken into account as a potential cause of anaemia with unknown aetiology. Low EPO levels, particularly when combined with a low iron status, are a sign that renal function will rapidly decline.	Yohei Fujita et al. [2019] [29]
22	Diabetes and pre-diabetes in the adult population of India: the role of anaemia and red cell indices in diagnosis	In order to establish diabetes or pre-diabetes, doctors must conduct further testing using plasma glucose levels when the hba1c is less than 7%. Hba1c should not be used to diagnose diabetes or pre-diabetes in patients with RDW >17; therefore, a 75gm OGTT should be used instead.	Subramanian Kannan et al. [2019] [30]
23	Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency	Diabetes was independently associated with anaemia, more so in men than in women, and may be connected to anemia's early emergence in people with moderate reduction in kidney function.	Tarek El-Achkar M et al. [2005] [31]
24	Red cell distribution width correlation with diabetic nephropathy	RDW levels should be assessed in patients with DR since they may be a simple and reliable predictive biomarker for increased inflammatory activity in Diabetic Retinopathy (DR) patients. Hemoglobin A1c and the duration of DM continue to be important risk factors for the development of DR. It is necessary to do more research and controlled trials with larger groups to examine the potential significance of serum RDW levels in DR patients.	Bengi Ece KURTUL et al. [2017] [32]
25	Red cell distribution width, as a biomarker in diabetes mellitus	There are a range of effects of hyperglycemia on red blood cells (RBC), including glycation of haemoglobin, reduced deformability, and shortened lifespan. Red cell distribution width (RDW) is a metric for erythrocyte volume heterogeneity. The purpose of this study was to investigate the associations between RDW and glucose, haemoglobin A1c (hba1c), and the prevalence of type 2 diabetes (DM). The findings of the study suggested that low RDW may be a surrogate marker of decreased RBC survival, with lower hba1c because of shorter duration of glucose exposure, and that low RDW is related with increased incidence of DM regardless of other risk variables. RDW is a biomarker that	G Engström et al. [2014] [33]

		could help those who are at risk of developing diabetes better identify their risk.	
26	RDW as a predictive marker of cardiovascular disease in diabetes patients	In individuals with cardiovascular diseases, red cell distribution width (RDW) has become a predictive indicator. Regarding baseline RDW, the study looked at diabetes patient mortality in the National Health and Nutrition Examination Survey. The RDW data was divided into four quartiles: Q1:12.4%, Q2: 12.5%–12.9%, Q3: 13.0%–13.7%, and Q4:>13.7%. RDW in Q4 was still significantly linked to all-cause mortality. RDW is a potent and independent marker for all-cause mortality and cardiovascular mortality in diabetic patients, according to the study's findings.	Sadeer G. Al-Kindi et al.[2017] [34]
27	Red cell distribution width in type 2 diabetic patients	RDW, which is currently thought of as an inflammatory marker with a considerable prognostic value of mortality in both diseased and healthy populations, is much higher in diabetic patients than in healthy people and is especially higher in uncontrolled glycemia. None of the investigated hypoglycemic medications had a discernible impact on RDW. Patients with diabetes and hypertension who are taking indapamide or thiazides and angiotensin receptor blockers together have RDW levels that are similar to those of the general population.	Aml Mohamed Nada [2015] [35]
28	Red blood cell distribution width as a prognostic marker in patients with heart failure and diabetes mellitus	Red blood cell distribution width is a simple to measure, widely accessible, and inexpensive marker in this study, demonstrated similar prognostic significance in the diabetic and non-diabetic group of heart failure (HF) patients with respect to the combined outcome of death from any cause or hospitalisation for HF. Between diabetic and non-diabetic patients, the RDW longitudinal alterations revealed a significant statistical difference. These findings may be attributable to the higher inflammatory burden that individuals with concurrent HF and diabetes mellitus (DM) may have compared to those with HF alone, and they may offer new insights into the pathophysiological mechanisms underlying the rise in RDW in HF and other pathological states, which are still not fully understood.	Andrew Xanthopoulos et al. [2017] [36]
29	Red Cell Distribution Width as inflammatory marker in Type 2 Diabetes Mellitus	In this study, diabetic patients with macrovascular complications were shown to have greater RDW (15.251±1.77) when compared to diabetic patients without macrovascular complications, with a statistically significant difference (p =0.04). Additionally, diabetic individuals with microvascular problems had higher RDW, but this finding was not statistically significant (p=0.87). With type 2 diabetes mellitus, high RDW levels are linked to an increased risk of macrovascular problems.	Heba Sherif et al. [2013] [37]

30	Red cell distribution width and erythrocyte osmotic stability in type 2 diabetes mellitus	The increase in red cell distribution width (RDW) that was seen in this study in both men and women with type 2 diabetes mellitus was mostly caused by lower iron levels in both groups. The decrease in iron is thought to have led to a decrease in MCHC and an increase in osmotic stability. Increased reticulocyte index as a result of decreased erythrocyte lifespan owing to high glucose environments typical of type 2 diabetes did not lead the MCV to decrease, as would be expected.	Maria Aparecida Knychala et al. [2021] [38]
31	RDW,RDW/MCV ratio as a predictor of diabetic ketoacidosis	Although red cell distribution width (RDW) and type 2 diabetes (T2DM) have been linked, information on diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar non-ketotic acidosis (HONK) is still unknown. RDW and the RDW/MCV ratio were discovered to be predictive of DKA and to be related with it. However, these variables were unhelpful for HONK prediction.	Atalay, H et al. [2018] [39]
32	Association between RDW ,macrovascular and microvascular complications in diabetes	In a nationally representative sample of USA individuals with diabetes, higher RDW values are linked to higher probabilities of acquiring cardiovascular disease and nephropathy. RDW, which is independent of conventional risk factors and the duration of the disease, may be a significant clinical indication of vascular problems in diabetes.	N Malandrino et al. [2012] [40]
33	Red blood cell parameters in diabetic patients	The 87 DMT2 patients who took part in this study were separated into two groups based on their hba1c levels: group A (n=41; presence in diabetics ≤6.5–6.9%) and group B (n=46; target in diabetes: ≥ 7.0%). Compared to group A, group B had significantly higher MCHC and RDW. RDW and MCHC could be used as supplemental markers of deteriorating glucoregulation.	Sadikuj Jaman et al. [2017] [41]
34	Anemia screening in diabetes patients	The current study's objective is to compare the haematological indices (RBC, HB, MCV, MCH, and MCHC) between diabetic patients and those with diabetic nephropathy. The study comprised 49 patients with diabetic nephropathy as cases and 49 diabetic patients as controls. Compared to diabetic controls, patients with diabetic nephropathy had significantly reduced haemoglobin, MCV, and MCHC levels. Because the severity of anaemia has a significant impact on the accuracy of blood glucose monitor measurements, the progression of complications from diabetes mellitus, and glycated haemoglobin levels, routine testing and treatment for anaemia in diabetic patients will improve the patient's quality of life.	Rajini Samuel et al. [2018] [42]
35	Hyperglycemia effect on red blood cells indices	According to this study, hyperglycemia results in an increase in the number of red blood cells, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC). RDW (red blood cell distribution width) was inversely correlated with inadequate glycemic management. RBC lifetime is simultaneously	Bader Alamri et al. [2019] [43]

Serial No:	AREA OF RESEARCH/ RESEARCH TITLE	FINDINGS/OUTCOMES	REFERENCE
1	In patients with diabetes and coronary artery disease, WBC count predicts heart failure.	In healthy individuals, a higher white blood cell (WBC) count increases mortality and coronary artery disease (CAD) risk. The goal of the study by Atsuhiko Kawabe et al. Was to find out if the WBC count in patients with Type 2 diabetes mellitus and established CAD predicts heart failure (HF) necessitating hospitalisation as well as all-	Kawabe, Atsuhiko et al. [2021][46]

		shortened by the coexistence of micro and microangiopathies with hyperglycemia.	
36	Hematological parameters in Diabetes Mellitus	According to the study's conclusions, diabetic individuals with poor control are more likely to develop anaemia. This highlights the importance of routine complete blood picture workups for the early diagnosis and treatment of anaemia in diabetic patients in the primary care setting to reduce associated morbidity from weakened immunity associated with anaemia and complications such diabetic ketoacidosis.	Rafae Farooqui et al.[2020] [44]
37	Anemia in patients with diabetic foot ulcer,	The frequency of anaemia in Nigerians with diabetic foot ulcers and its impact on disease outcome were researched, and it was discovered that 53.6% of patients had anaemia and that there was a substantial link between anaemia and poor wound healing, amputation, and mortality in their research subjects.	Ibrahim D.Gezawa et al. [2019][45]

Table 2 : Relevant studies on White blood cell count, Neutrophil-Lymphocyte ratio in diabetes mellitus patients

		cause death, acute myocardial infarction (AMI), and stroke. In patients with concurrent Type 2 diabetes mellitus and established CAD, the study found that a greater WBC count is a predictor of hospitalisation for heart failure, all-cause death, and acute myocardial infarction but not for stroke.	
2	Type 2 diabetes prevalence and white blood cell count in young males	The study by Gilad Twig et al. [2013] examined whether WBC count is an independent risk factor for diabetes incidence among young, healthy adults and concluded that WBC count, a widely used and accessible test, is an independent risk factor for diabetes in young men at values well within the normal range.	Gilad Twig et al. [2013][47]
3	The association between Type 2 diabetes mellitus and the neutrophil-to-lymphocyte ratio and diabetic peripheral neuropathy	Results showed that Neutrophil Lymphocyte Ratio (NLR) and diabetic peripheral neuropathy (DPN) have a significant correlation, suggesting that NLR may be an independent risk factor for DPN.	Tingting Xu et al [2017] [48]
4	Association between type 2 diabetes mellitus hyperuricemia and neutrophil-to-lymphocyte ratio	Increased NLR can show the immune system's functionality during chronic inflammation.	Peng Luo et al [2016] [49]
5	Neutrophil-to-lymphocyte ratio predictive value healing of diabetic wounds	A substitute marker for systemic inflammation is the neutrophil-to-lymphocyte ratio (NLR). The relationship between NLR and wound healing in diabetic wounds was researched by Nasibeh Vatankhah et al. Higher chances of nonhealing were correlated with greater NLR. The study found that NLR, which is independent of wound infection and other variables, can predict the likelihood that diabetic foot ulcers would heal completely.	Nasibeh Vatankhah et al.[2017] [50]
6	The neutrophil-to-lymphocyte ratio's long-term prognostic value in Type 2 diabetes patients who present with acute myocardial infarction	After an acute myocardial infarction (AMI), patients with diabetes mellitus experience worse long-term results than non-diabetics. The study concluded that in diabetics, increased NLR post-AMI is an independent predictor of significant adverse cardiac events. Monitoring this readily available new index enables risk categorization and prognostication.	Lee GK et al. [2012] [51]
7	Neutrophil-lymphocyte ratio study as a novel marker of diabetic nephropathy in type 2 diabetes	Diabetes can lead to a microvascular condition called diabetic nephropathy (DN). The findings of an investigation by Ashok Rao et al. Indicated that DN and neutrophil lymphocyte ratio had a strong relationship. As a result, NLR may be seen of as a new early-stage surrogate marker of DN. Patients with type 2 DM and elevated albuminuria showed a significant and independent increase in NLR. NLR may therefore be considered as a risk indicator and predictor of DN.	Ashok Rao et al [2017] [52]
8	Study of the link between diabetes complications and WBC count	The development of micro and macro vascular problems in patients with type 2 diabetes can be predicted by a higher leukocyte count, even if it is within the normal range.	Mohit Naredi et al. [2017] [53]

9	Neutrophil-Lymphocyte Ratio and Microvascular Complications in Type 2 Diabetes Patients from Egypt	The Unit of Diabetes & Metabolism at the Faculty of Medicine, Alexandria University, Alexandria, Egypt conducted a study on 280 subjects intending to examine the relationship between type 2 diabetic patients' diabetic retinopathy, nephropathy, neuropathy, and neutrophil-lymphocyte ratio and their microvascular complications. The study's findings showed that diabetic patients with retinopathy, neuropathy, and nephropathy had neutrophil-lymphocyte ratios (NLR) that were significantly greater than those of diabetic patients without any microvascular problems and of the healthy control group. This study concluded that the neutrophil-lymphocyte ratio (NLR), an effective, simple, and stable marker of inflammation, can be a significant predictor of the existence of microvascular problems in type 2 diabetic patients from Egypt.	Eman Youssef et al [2015] [54]
10	Epicardial adipose tissue, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio association with diabetic nephropathy.	Simple, low-cost indicators of inflammation include the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). In this cross-sectional study, 200 diabetes patients were involved. Depending on the patients' degrees of albuminuria, the patients were divided into three groups. The NLR and PLR were calculated using a complete blood count, and it was concluded that this method can help predict albuminuria and inflammation in diabetic patients.	Emin Murat Akbas et al. [2014] [55]
11	Platelet-lymphocyte ratio and neutrophil-lymphocyte ratio as new indicators of diabetic nephropathy in type 2 diabetes patients	Increased neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were found to be significantly correlated with diabetic nephropathy in a study of 158 diabetic patients. These findings suggest that these parameters may serve as both a predictor and a prognostic risk marker for diabetic nephropathy.	Marwa Jaaban et al. [2021] [56]
12	Neutrophil to lymphocyte ratio as a measure of type 2 diabetes mellitus's diabetic control level	Chronic low-grade inflammation is linked to type 2 diabetes mellitus. Hemogram-derived neutrophil to lymphocyte ratio is one of the novel inflammatory markers (NLR). The goal of the study was to compare the NLR levels of diabetic subjects and healthy controls and to look for any potential relationships between NLR and hba1c. It was found that elevated NLR in otherwise healthy subjects may be a sign of underlying impaired glucose metabolism, and that NLR should also be used as a marker of diabetic control level in type 2 diabetic subjects in addition to hba1c.	Tuba T Duman et al. [2019] [57]
13	Investigation of neutrophil lymphocyte ratio and blood glucose regulation in type 2 diabetic patients	Blood glucose control and NLR may be significantly related. The authors speculate that patients with type 2 diabetes mellitus may have elevated hba1c levels and increased NLR.	Fatih Sefil et al. [2014] [58]
14	In Chinese middle-aged and older individuals, an elevated white blood cell count is linked to an increased risk	Even when the WBC level was within the normal range, an elevated circulating WBC count was linked to a deterioration in glucose metabolism. An elevated WBC count may signal an increased risk of T2DM and impaired glycemic control. For the purpose of developing future diabetes prevention and treatment strategies, it is important to understand the function of inflammation in	Hua Jiang et al. [2014] [59]

	of disorders of glucose metabolism.	the onset of the disease.	
15	Relationship between the neutrophil-to-lymphocyte ratio and diabetic complications in adults with diabetes.	Other than diabetic retinopathy, a higher Neutrophil-Lymphocyte Ratio ratio was associated with a greater prevalence of cardiovascular disease and diabetic kidney disease in diabetic individuals.	Heng Wan et al. [2020] [60]
6	Diabetes patients' platelet-lymphocyte ratio is linked to depression	Patients with Diabetes mellitus (DM) are prone to depression, and it has been previously established that there is a very high comorbidity incidence between depression and DM. In order to determine the relationship between PLR and depression, this study examined patients with diabetes mellitus (DM) and the platelet-lymphocyte ratio (PLR) in these individuals. It concluded that PLR is an independent risk factor for clinically relevant depression (CRD) in DM patients, and the relationship between them is nonlinear. Patients with diabetes had the lowest incidence of depression when PLR was close to 69.2. The nonlinear association between PLR and depression in DM patients requires more investigation.	Depu Zhou et al. [2021] [61]

Table 3: Relevant studies platelets ,platelet indices and hemogram derived ratios in diabetes mellitus

patientsSerial No:	AREA OF RESEARCH/ RESEARCH TITLE	FINDINGS/OUTCOMES	REFERENCE
1	Platelet indices and CRP in diabetes patients' vascular complications	In patients with diabetes, altered platelet morphology and functions are linked to pathological processes and an increased risk of vascular problems. In order to understand the pathophysiology of vascular problems in type 2 diabetes patients, the study set out to determine the relationship between platelet indices, fasting blood sugar, HbA1c, and hs-CRP levels. A high HbA1c level is strongly connected with poor glycemic management. Increased MPV, PDW, and raised hs-CRP readings may also be used as a confirmatory test to determine the confirmatory test in findings of developing complications	Farah Jabeen et al [2013] [62]
2	Platelets Indices as Biomarkers for Glycemic Management and Complication Progression in Type 2 Diabetes Mellitus Patients	The major goal of this study was to compare several platelet parameters between patients with diabetes mellitus type 1 (without and with complications) and controls. The study's findings demonstrated that all platelet parameters, such as mean platelet volume (MPV), platelet-large cell ratio, platelet distribution width (PDW), and platelet crit, were significantly altered among patients with DM type 2 complications when compared to other	Shahzad Ali Jiskani et al. [2021] [63]

		groups, and they suggested that platelet indices could be used as a simple and affordable tool for monitoring the development of complications in diabetic mellitus type 2 patients.	
3	Platelet indices in type 1 diabetes mellitus	T1DM patients have higher levels of platelet indices, which are common, simple to use, and inexpensive hemogram measures. When these findings are confirmed by more extensive research, this could result in the change of treatment plans based on the outcomes of these indices.	Isa Sincer et al. [2019] [64]
4	Platelet volume indices as prognostic biomarkers for diabetic complications in Type 2 diabetic patients	According to the study, MPV and PDW have increased in all of these diabetic high-risk populations. This suggested that elevated MPV and PDW may serve as biomarkers for the early diagnosis of potential complications. They discovered that relative to macrovascular issues, these platelet indices were statistically more significant in microvascular complications . The statistical relevance of P-LCR in predicting diabetes complications was low.	Archana Buch et al. [2017] [65]
5	Can platelet parameters be used to assess glycemic control or the development of complications in type 2 diabetes mellitus?	In DM with complication, all platelet parameters were found to be greater than in DM without complication, and this difference was found to be statistically significant. The study's findings suggested that different platelet indices might be used as an easy-to-use, reasonably priced tool to track the development and management of diabetes.	Mukta Pujani et al.[2018] [66]
6	Platelet indices in diabetics and influence of glycemic control	Early in the course of the disease, platelets from patients with type 1 and type 2 diabetes display increased platelet aggregation activity, which may be a precursor to the onset of cardiovascular disorders. The increased cardiovascular risk in diabetes patients appears to be considerably influenced by both atherosclerosis and thrombosis. Platelet indices include mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR). Platelet indices are significantly higher in diabetics, and the extent of the increase is greater in diabetics with poor glycemic control, according to a study conducted in a tertiary health care facility in North East India.	Prasun Bhattacharjee et al.[2016] [67]
7	Platelet indices as a predictor of microvascular complications in type 2 diabetes	Patients with type 2 diabetes mellitus (T2DM) are more likely to experience micro- and macrovascular problems, which lower quality of life and increase morbidity. A total of 125 diabetic patients who attended the diabetes OPD and were admitted to the medical department, along with non-diabetic controls with similar ages and sexes, were studied. Diabetes patients had significantly higher MPV, PCT, PDW, and P/LCR values than did controls who were	Rajas S. Walinjkar et al. [2021] [68]

		the same age and gender. Additionally, when compared to diabetic participants without microvascular complications, the rise in MPV, PDW, and P/LCR was more substantial in diabetic subjects with microvascular complications. Additionally, platelet dysfunction revealed a positive correlation with HbA1C, retinopathy, nephropathy, and neuropathy separately. Statistics revealed that variations in platelet indices were statistically linked to diabetes and its consequences.	
8	Platelet indices in diabetes mellitus: Signs of diabetic microvascular complications	Diabetes patients' MPV, PDW, and platelet-large cell ratios were all considerably greater than those of the control subjects. PDW in diabetics differs between patients and controls as well as between diabetics with and without microvascular problems. It was higher in individuals with complications compared to those without complications. PDW and MPV discriminant analysis could classify the majority of individuals with diabetes problems.	Sonali Jindal et al.[2011] [69]
9	Mean Platelet Volume to Lymphocyte Ratio as a Novel Marker for Diabetic Nephropathy	The goal of the study was to compare the mean platelet volume to lymphocyte ratio (MPVLR) of diabetic nephropathy subjects to that of diabetics without diabetic nephropathy. The study found that MPVLR is an easily calculated and efficient index that can be thought of as a potent and independent predictor of diabetic nephropathy in diabetic patients. The authors claimed that it could be a helpful supplemental test for the diagnosis of diabetic nephropathy.	Mehmet Zahid Kocak et al. [2018] [70]
10	Independent of HbA1c level, mean platelet volume increases in type 2 diabetes mellitus.	Hemogram measures that may be linked to inflammation include mean platelet volume and red cell distribution width. Researchers compared the hemogram characteristics of type 2 diabetic patients to those of healthy participants retrospectively, however they were unable to identify any significant differences in RDW levels between the two groups. On the other hand, MPV levels were significantly higher elevated in the study group than in the control group, suggesting an association between MPV and type 2 diabetes mellitus. To establish the connection between MPV and the degree of metabolic control, prospective studies, including a bigger cohort are required.	Lutfullah cakir et al. [2014] [71]
11	Mean platelet volume and platelet counts in type 2 Diabetes	Indicators of thrombotic potentials and risk factors for microvascular problems in diabetics include mean platelet volume and platelet counts. The goal of this study was to compare platelet counts and mean platelet volumes between type 2 diabetic patients receiving treatment and non-diabetic controls. The results showed that	Akinbami Akinsegun et al. [2014] [72]

		mean platelet counts were higher in the treated diabetics than in the non-diabetic controls, while mean platelet volumes were lower in the cases. Although diabetics were receiving treatment, both indicators were within the usual range for healthy people.	
12	Diabetes patients with and without diabetic foot ulcers are compared using platelet indices.	Increased platelet indices in diabetic patients with diabetic foot ulcers were shown indicating more reactive and aggregatable platelet function.	A I Mardia et al. [2018] [73]
13	Comparison of the mean platelet volume among patients with diabetes mellitus, individuals with impaired fasting blood sugar, and non diabetic subjects	Patients with diabetes mellitus and impaired fasting glucose have significantly higher Mean platelet volume levels.	Zuberi B F et al. [2008] [74]
14	Prognostic significance of platelet indices	The metrics that are most frequently assessed are mean platelet volume (MPV), platelet diversity index (PDW), platelet crit (PCT), and the presence of bigger platelets (P-LCRs platelet larger cell ratio). Patients with malignancy, myocardial infarction, type 2 diabetes mellitus, or acute surgical diseases including appendicitis have higher platelet indices (PI) readings. The measurement of PIs does not incur additional costs and can be carried out as part of a routine cell blood count without the need for extra blood samples. Platelet indices may be prognostic and predictive in a wide range of situations, the study found.	Karolina Pogorzelska et al. [2020] [75]
15	Are platelet indices helpful in assessing patients with type 2 diabetes??	The results of the study indicate significant changes in platelet properties in patients with T2DM, which may indicate that this population has more reactive and aggregatable platelets. Given that platelet examination is a simple and affordable technology, these findings imply that it may be helpful in the early detection of long-term complications in diabetes patients.	Kamilla R. Alhadas et al. [2016] [76]

The purpose of the study by Dragana Milosevic et al [2019] was to identify potential changes in the CBC parameters dependent on glycemic management in individuals with Type 2 diabetes (T2DM). Based on the study's findings, it may be concluded that several CBC measures, such as platelets, WBC, PCT, MPM, PMDW, and HCT, could be helpful tools in monitoring T2DM and potential markers of its complications. The results of the study suggest that haematological indices are simple, affordable, valuable, and easily available laboratory parameters that might be used in healthcare facilities. Therefore, general practitioners are the first line of care for T2DM patients who use these indicators in everyday practice for diagnosis and follow-up [77]

The results by Hussen Ebrahim et al. [2022] showed a statistically significant difference between the healthy control group and those with type 2 diabetes in terms of the mean and SD of the monocyte count, basophil count, monocyte percentage, basophil percentage, RBC count, Hct, MCV, MCH, RDW-SD, MPV, and plateletcrit. While RBC count, Hemoglobin level, Hct, MCV, MCH, and RDW-SD were statistically negatively correlated with fasting blood sugar in T2DM patients, WBC count,

neutrophil count, monocyte count, basophil count, PDW, MPV, PLC-R, and plateletcrit were statistically favourably correlated with FBG. [78].

The study by Belete Biadgo et al. [2016] found statistically significant differences between diabetic patients and healthy individuals in various haematological parameters. Between diabetic patients and healthy individuals, there was a significant difference in the width of the red blood cell distribution (47.3±2.6 fL vs 45.2±3 fL)). Absolute neutrophil, absolute lymphocyte counts and total white blood cells were considerably increased in diabetic patients compared to controls. Mean platelet volume and platelet distribution width were found to be considerably higher in diabetes individuals among the platelet indices. Hematological indices may therefore be helpful markers of vascular complications and glycemic management in people with type 2 diabetes [79].

Satilmis Bilgin et al. [2020] studied on metabolic parameters and novel inflammatory markers derived from hemogram indices in type 2 diabetic men. The study highlighted that diabetes-related men should have their HbA1c levels measured if they have elevated RDW, NLR, MLR, MPR, or RPR levels because each of these variables has a substantial correlation with HbA1c. Furthermore, elevated RDW, NLR, MLR, RPR, and MPR levels may be indicators of worse diabetes management in men with type 2 diabetes mellitus [80].

A study on 137 type II diabetic individuals found abnormal WBC, hemoglobin, Hematocrit, and MCH levels. Uncontrolled hyperglycemia was linked to greater leucocyte levels. The pathophysiology and development of these complications associated with diabetes may be linked to the chronic inflammation that can be revealed by this factor when combined with other markers. A complete blood count test could be regarded as a suitable clinical assessment for the early detection and prevention of microvascular and macrovascular problems, hence lowering morbidity and mortality from diabetes mellitus [81].

The goal of the study by Mehmet Akif Sargın et al. [2016] was to determine whether the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) might be used to screen for gestational diabetes mellitus (GDM). The researchers concluded that these tests not be applied to check for GDM. However, a rise in leukocyte count is a significant marker of GDM since it provides evidence of undiagnosed subclinical inflammation [82] .

Although the platelet-to-lymphocyte ratio was lower in hyperglycemic participants, their neutrophil-to-lymphocyte ratio was comparable to that of normoglycemic subjects. The significance of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in the hyperglycemic state, as well as their predictive value, will be determined by future prospective investigations. Brena Barros Mendes et al. [2019] [83]

Jin-Rui Wang et al. [2020] studied correlation between neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and diabetic retinopathy among diabetic patients without a family history and highlighted that NLR and PLR, two markers of systemic inflammation, are closely associated with diabetic retinopathy in individuals with type 2 diabetes who do not have a family history of diabetes or hypertension (DR). Higher NLR and PLR enhance the chance of developing DR, and when paired with hemoglobin markers, they helped reclassify DR [84].

The purpose of the study by Burcin Atak et al. [2019]was to compare the platelet-to-lymphocyte ratio (PLR), a novel inflammatory measure obtained from hemogram, in diabetic patients to those in healthy volunteers. PLR may be helpful in predicting the onset and control levels of type 2 diabetes mellitus because it is a low-cost and simple to use indicator. However, bigger prospective studies are required to confirm its connection with HbA1c [85].

H.Atli et al.[2022] studied on the predictive value of hematological and inflammatory data in diabetic and non-diabetic retinopathy found that both diabetic and non-diabetic retinopathy have higher levels of IL-6 and TNF- α. Additionally, proliferative diabetic retinopathy had higher median neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) values than other groups. These results suggest that the inflammatory process may accelerate the progression of retinopathy [86].

5. Discussion

According to some of the research studies, anemia frequently coexists with diabetes mellitus because of various contributing factors suggesting anemia screening should be done on diabetes patients, which helps in improving the overall care of diabetes patients. While treating diabetic patients, the treating physicians should know the effects of the medication, including the oxidative stress and anaemia caused by metformin, vitamin B12 deficiency brought on by metformin use, and drug-induced hemolytic anaemia.The key findings on the study by Takashi Maruyama et al. [2019]

highlighted that in patients with impaired kidney function, canagliflozin therapy improved erythropoiesis. Further research is required to clarify this, however, as the present study had a limited sample size and no comparison group. The effect on erythropoiesis appears to be caused by an EPO production-mediated mechanism and might be independent of glycemic management [87].More researches should be carried out on side effects of metformin on long term and the alternatives which can be used.

Many of the studies suggested red cell distribution width (RDW)to be used as

- Predictive marker of inflammatory process in diabetic patients
- Low RDW may be a surrogate marker of decreased RBC survival
- RDW as a potent and independent marker for all-cause mortality and cardiovascular mortality in diabetic patients
- Red blood cell distribution width as a prognostic marker in patients with heart failure and diabetes mellitus
- RDW as a predictor in diabetic complications
- RDW and the RDW/MCV ratio were discovered to be predictive of Diabetic ketoacidosis
- RDW (red blood cell distribution width) was inverse correlation with inadequate glycemic management.
- RDW and MCHC as supplemental markers of deteriorating glucoregulation.

Few of the research articles used white blood cell count as a predictor of impaired glycemic control and an increased risk of T2DM. In healthy individuals, a higher white blood cell (WBC) count increases mortality and coronary artery disease (CAD) risk. Kawabe, Atsuhiko et al. [2021] emphasised that in patients with diabetes and coronary artery disease, WBC count predicts heart failure. Neutrophil-lymphocyte ratio was used on many studies as a novel predictive and prognostic marker in diabetes and its complications. Study on platelet and platelet indices were carried out by some researchers to use as biomarkers of glycemic control, predictor of vascular complications, its prognostic significance.

6. Conclusion

Better understanding of hematological changes in diabetic patients along with complete blood count, hemogram indices and novel hemogram derived indices, researches on Neutrophil-Lymphocyte ratio (NLR), Monocyte-Lymphocyte ratio (MLR),Red cell distribution width-Platelet ratio (RPR),Mean Platelet Volume to Lymphocyte Ratio (MPVLR) Platelet-Lymphocyte ratio (PLR) etc may provide new insight into a new approach to treat diabetic patients in order to enhance glycemic control and use these markers as a predictor of diabetic complications. Using simple, cost-effective CBC and hemogram markers will help physicians in early detection of diabetes and its long term complications. Along with diabetes management ,anemia screening should be included in diabetic patients to improve overall management of diabetes patients However, studies on a bigger cohort are required to establish the diagnostic and prognostic value of complete blood count and hemogram-derived novel markers in diabetes mellitus and its complications.

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