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Evaluation of Platelet Indices in Patients with Type 2 Diabetes Mellitus in Atbara City 2018

Supplementary research for attainment B.Sc. and privilege degree in medical laboratory department

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يسم الله الرحمن الرحيم

الآية

(وَأَنزَلَ اللَّهُ عَلَيْكَ الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا)

صدق الله العظيم

(سورة النساء. الآية رقم ١١٣)

Dedication

To our mothers and fathers who spent all the life to help us.

To our sisters and brothers and friends.

To souls of all Sudanese who died by reduction health care.

To any one helped us to complete this research.

Acknowledgements

- First of all thanks to Allah for given us the power and willing to complete this study.

- Our deep and great thanks to the Administration of Laboratory Department in Health Insurance Complex for their material and scientific support that helped us finishing this study.

List of Abbreviations

DM	Diabetes mellitus
FG	Fibrinogen
GDM	Gestational DM
ICAM	Intracellular adhesion molecules
IDDM	Insulin dependent diabetes mellitus
JP3	Inositol triphosphate
LFA-1	Lymphocyte function associated antigen
MLCK	Myosin light chain kinase
MPV	Mean platelet volume
NIDDM	Non-insulin dependent diabetes mellitus
NSAI	Non-steroidal anti-inflammatory agent
PDW	Platelet distribution width
PKC	Protein kinase C
PLA2	Phospholipase A2
PSGL-1	p.selective glycoprotein ligand-1
T2DM	Type2 diabetes mellitus
TXA2	Thromboxane A2
VWF	Von willebrand factor

Abstract

Back ground:

DM patients are at a high risk of developing micro and macro vascular disease. Mean platelet volume (MPV) and platelet distribution width (PDW) are indicators of PLT function and activity and they have been reported to be influenced significantly by diabetes.

This analytical cross sectional study aimed to assess the Plt indices in type2 DM in 50 of Sudanese diabetic patient and 50 healthy as control group; males and females (30-75) years old, in Atbara River Nile state the study period was from March to July 2018.

Methodology:

Venous blood (2.5) ml were collected in EDTA container under ideal condition and analyzed by automated cell counter (SysmexKX-2IN) and thin blood film .

Result:

The Data was analyzed by SPSS software (statistical package for social science) and the result showed that MPV and PDW values were significantly elevated in diabetic patients compared to control subjects (p=0.002) (p=0.006) respectively, mean platelets volume (3.76) and for platelet distribution width (٢,٣٨).

Conclusion:

This study concluded a higher mean platelet volume and platelet distribution width in diabetic patients than controls.

المستخلص

الخلفية:

مرضى السكري هم في خطر كبير لتطوير مرض الأوعية الدموية الصغرى والكبرى. متوسط حجم الصفائح الدموية (MPV) وعرض توزيع الصفيحات (PDW) هي مؤشرات دالة ونشاط PLT وقد تم الإبلاغ عن أنها تتأثر بشكل كبير بمرض السكري.

هذه دراسة وصفية مقطعية تهدف لقياس مستشعرات نشاط الصفائح الدموية في ٥٠ من المرضى السودانيين المصابين بمرض السكري النوع الثاني و ٥٠ من مجموعة قياسية من الاصحاء ذكور وإناث (٣٠-٧٠) عام ، أجريت في مستشفى عطبرة ولاية نهر النيل في خلال الفترة من مارس ٢٠١٨ الي يوليو ٢٠١٨ .

الطريقة والمواد:

تم جمع٢,٥ مل من الدم الوريدي في مضاد التجلط وتم تحليلها بجهاز (Sysmex KX-2IN) وتم فرد الأفلام على شرائح زجاجية.

النتائج:

تم تحليل البيانات بواسطة برنامج الحزم الإحصائية للعلوم الاجتماعية وأظهرت نتائج هذه الدراسة أن مستويات متوسط حجم الصفائح الدموية (٣,٧٦) ومتوسط عرض توزيع الصفائح الدموية (٢,٣٨) أعلي عند مرضي السكري علي التوالي (p= 0.006)(p=0.002) مقارنة بمجوعة التحكم.

الخلاصة:

خلصت الدراسة إلى ارتفاع حجم الصفائح الدموية ومتوسط عرض توزيع الصفائح الدموية لدى مرضى السكري مقارنة بالأصحاء.

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1. Introduction and Literature Review

1.1 Introduction

1.1 .1 Diabetes Mellitus:

1.1.1.1 Definition:

Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago (1). In 1936, the distinction between type 1 and type 2 DM was clearly made (2). Type 2 DM was first described as a component of metabolic syndrome in 1988(3). Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DMcharacterized by hyperglycemia, insulin resistance, and relative insulin deficiency(4). Type 2 DM results from interaction between genetic, environmental and behavioral risk factors (5, 6). People living with type 2 DM are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death(6).

1.1.1.2 Incidence of Diabetes Mellitus:

Worldwide, over 140 million people suffer from diabetes making this one of the most common diseases (7). In the Western population the prevalence of DM has been estimated to be 3-5% and the incidence is rapidly growing up and will be more than doubled within 15 years (7). Type II DM accounts for more than 80 % cases of DM and is slow-onset, heterogeneous disorder, resulting from interactions between environmental factors and polygenetic inheritance (7).

1.1.1.3 Classifications of Diabetes Mellitus:

The World Health Organization guidelines recommend the following categories of diabetes: type 1, type 2, and gestational diabetes, and other specific types of diabetes. Type 1 or juvenile, diabetes mellitus mainly affects children and adolescents and is due to absolute or severe shortage of insulin (8). It is usually due autoimmune destruction of pancreatic beta cells which

produce insulin. This makes it necessary for the patient to depend on insulin therapy- hence the name insulin dependent diabetes mellitus (IDDM). Type 2 or maturity onset, is caused by a combination of peripheral resistance to insulin action and inadequate compensatory response to insulin secretion" relative insulin deficiency"(8). The patient may require insulin or may not need if the pancreas can be stimulated by

oral hypoglycemic agents- hence the name non-insulin dependent diabetes mellitus (NIDDM).Gestational diabetes mellitus is any degree of glucose intolerance with onset or first recognition during pregnancy. GDM is carbohydrate intolerance with onset or first recognition in pregnancy (8). Up to 70% of affected women will manifest type 2 diabetes mellitus within 10 years thereafter. The causes of GDM include metabolic and hormonal changes patients with GDM frequently return to normal postpartum. The other specific types associated with certain conditions (secondary) including genetic defects of beta cell functions or insulin action, pancreatic disease, diseases of endocrine origin, drug or chemical induced insulin receptor abnormalities, and certain genetic syndromes (8).

1.1.1.4 Pathophysiology of Type2 DM:

Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure (9, 10) this leads to a decrease in glucose transport into the liver, muscle cells, and fat cells.Here is an increase in the breakdown of fat with hyperglycemia. The involvement of impaired alpha-cell function has recently been recognized in the pathophysiology of type 2 DM (11). As a result of this dysfunction, glucagon and hepatic glucose levels that rise during fasting are not suppressed with a meal.

Given inadequate levels of insulin and increased insulin resistance, hyperglycemiaresults (11).

1.1.1.5 Complications of Diabetes Mellitus:

Long –standing diabetes mellitus inevitably leads to the development of vascular, renal and other pathologies. Some common long- term effects of DM include vascular complications (such as atherosclerosis, ischemic heart disease, ischemia and gangrene of foot and microangiopathy),diabetic nephropathy (glomerulr damage and renal failure), eye change (diabetic retinopathy and cataract), and nervous defect (12).

1.1.1.6 Diabetes Mellitus and Vascular Disease:

Diabetes is associated with accelerated rates of thrombosis, circulatory dysfunction, and atherosclerosis.Most of the morbidity and mortality seen in patients with diabetes mellitus, especially in type 2 (non-insulin dependent) diabetes, is the result of micro – and macro – vascular occlusive disease in which thrombosis play an important part (13).

1.1.2 Platelet:

1.1.2.1 Platelet Production (Megakaryopoiesis and Thrombopoiesis):

Platelets are produced in the bone marrow by fragmentation of the cytoplasm of megakaryocytes. The precursor of the megakaryocyte the megakaryoblast arises by a process of differentiation from haemopoietic stem cells (14). The megakaryocytes mature by endomitotic synchronous nuclear replication, enlarging cytoplasm volume as the number of nuclear lobes increases in multiples of two. At variable stages in development most commonly at eight nucleus stage the cytoplasm become granular and platelets are liberated (14). Platelet production follows formation of micro-vesicles in the cytoplasm of the cell which coalesce to form platelet demarcation membrane. Each megakaryocyte is responsible for the production of about 4000 platelets (14).

1.1.2.2 Circulating Platelets and their Life Span:

In steady state, when platelet production equals destruction, platelet turnover has been estimated at 1.2 to 1.5 × 1011 cells per day (15). The sites for platelet removal appear to be the spleen, the liver, and the bone marrow. The

platelet count varies among the healthy population (1.5 to 3.5 X 105/μl) but remains within a fairly narrow range in any given individual (16).

1.1.2.3 Platelet Structural and Functional Anatomy:

In describing detailed platelet anatomy, most information is derived from transmission electron microscopy, and platelet structure is classified into four general areas:

1. The platelet surface.
2. The membranous structure.
3. The cytoskeleton (17).
4. The granules (18).

1.1.2.4 Platelet Surface:

The platelet surface includes the plasma membrane that separates intra- from extra cellular regions, it is exceptionally complex in composition, distribution and function, incorporating a number of glycoproteins and lipids into is phospholipids bilayer and integrating a variety of extra- and intra-platelet events such as permeability, agonist stimulation, and platelet adhesion, activation\secretion, and aggregation; and the glycocolyx that is a fuzzy layer of lipids, sugars, and proteins, coats the outside surface of the platelet plasma membrane, including the surface-connected tubular system, and interacts with both the plasma and the cellular components of the blood and blood vessels (18).

Platelets possess different types of surface molecules which interact with corresponding molecules on platelets and other cells such as intercellular adhesion molecule (ICAM), Von Willebrand factor (vWF), fibrinogen (FG), lymphocyte function-associated antigen-1 (LFA-1), and P-selectinglycoprotein ligand-1 (PSGL-1).The Glycoprotein IIb/IIIa integrin constitutes the most abundant platelet adhesion receptor (16). The GIIb/IIIa receptor is an important molecule for the aggregation of platelets and platelet-neutrophil-interaction. Upon activation, platelet GPIIb/IIIa binds soluble

extracellular adhesion molecules, such as vWF, fibrinogen, fibronectin, and thrombospondin. The absence of GPIIa/IIIb in Glanzmansthrombasthenia is associated with a severe bleeding due to defective platelet aggregation and clot retraction (16).

1.1.2.5 Platelet Granules:

Considering platelet granules and organelles, platelet process secretary granules and mechanisms that serve these purpose by releasing additional stimulatory materials previously sequestered within the resting platelet, into the environment for developing a haemostatic or thrombotic mass. Two main secretary granules, the alpha granules and dense bodies, appear to be the main effectors with their highly reactive and readily available contents (18). The role of these other platelet granules (lysosomes, peroxisomes) and organelles such as mitochondria is less dramatic than those of the alpha granules and dense bodies (18).

1.1.2.6 Platelet Function:

The main function of platelets is the formation of mechanical plugs during the normal haemostatic response to vascular injury. In the absence of platelets spontaneous leakage of blood through small vessels may occur (19). Central to their function are platelets activation, adhesion, secretion, aggregation, fusion and procoagulantactivity (19). Other functions for platelets are also known: stimulation of leucocytes to accumulate around the platelet plug; that is, they may release chemotactic substances, release of some vasoactive aminesand transportation of serotonin from sites of synthesis to other sites of function (19).

1.1.2.7 Platelet Activation:

Physiologic stimuli that can activate platelets both in vivo and in vitro are amazingly diverse. Substances shown to produce this reaction include materials as diverse as proteolytic and structural proteins (such as thrombin and collagen), vasoactive material (such as serotonin and epinephrine),

nucleotides (such as ADP), polypeptides hormones (such as vasopressin), and non-biologic surfaces (such as glass and latex particles) (20). Other stimuli arise under pathologic conditions. Among these are antigen-antibody complexes or aggregated gamma globulins that react with an Fc receptor on human platelets and a complement receptor on rabbit platelets (20). The responses to these stimuli are initiated when the agonists bind to specific receptors on the plasma membrane (20).

Platelets respond to a variety of substances by changing their shape, and then become sticky so that they aggregate if brought into contact by stirring, and finally secrete the contents (20).

1.1.2.8 Platelet Shape Change:

Most stimuli cause a change in shape and this change involves first the formation of very fine pseudopodia (i.e., filopodia) from the rim of the disc, followed by a general "rounding up" of the platelet so that it becomes a spiny sphere, often with much broader pseudopodia (21).Platelet shape change can be measured in vitro by flowcytometry or electron microscopy. Shape change with or without secretion causes the microtubule bundle that lies beneath the rim of the disk to become centralized and surround the platelet granules, which are consequently concentrated toward the center of the platelet (20).

1.1.2.9 Platelet Adhesion:

The adhesion of platelets to the collagen exposed on endothelial cell surfaces is mediated by Von Willebrand factor (22).

The function of vWF is to act as a bridge between a specific glycoprotein on the surface of platelets (GPIb/IX) and collagen fibrils. In addition to its role as a bridge between platelets and exposed collagen on endothelial surfaces. Adhesion to this surface is associated with loss of granules (i.e., secretion), which is not inhibited by non-steroidal anti-inflammatory (NSAI) agents (23).

1.1.2.10 Platelet release reaction:

Collagen exposure or thrombin action results in the secretion of platelet granule content. The initial activation of platelets is induced by thrombin binding to specific receptors on the surface of platelets, thereby initiating a signal transduction cascade. The thrombin receptor is coupled to a G-protein that, in turn, activates phospholipase C-g (PLC-g). PLC-g hydrolyzes phosphatidylinositol-4, 5-bisphosphate (PIP2) leading to the formation of inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 induces the release of intracellular Ca2+ stores, and DAG activates protein kinase C (PKC) (21).The collagen to which platelets adhere as well as the release of intracellular Ca2+ leads to the activation of phospholipase A2 (PLA2), which then hydrolyzes membrane phospholipids, leading to liberation of Arachidonic acid (24). Arachidonic acid release leads to an increase in the production and subsequent release of thromboxane A2 (TXA2). TXA2 is a potent vasoconstrictor and inducer of platelet aggregation by lowering platelet cAMP. The release reaction is inhibited by substances which increase the levels of cAMP. One such substances, is the prostaglandin prostacyclin (PGI2) which is synthesized by vascular endothelial cells. It is a potent inhibitor of platelet aggregation and prevents their deposition on normal vascular endothelium (25).

1.1.2.11 Platelet Aggregation:

ADP, thrombin, serotonin, vasopressin, and epinephrine initiate aggregation within a few seconds. Fluid-phase calcium or magnesium is necessary for aggregation. In addition, fibrinogen is also required. With ADP or epinephrine, this protein must be present in the suspension medium, whereas with thrombin or collagen it is secreted from the alpha granules (26).

Another enzyme activated by the released intracellular Ca2+ stores is myosin light chain kinase (MLCK). Activated MLCK phosphorylates the light chain of myosin which then interacts with actin, resulting in altered platelet

morphology and motility. One of the many effects of PKC is the phosphorylation and activation of a specific 47,000-Dalton platelet protein. This activated protein induces the release of platelet granule contents; one of which is ADP. ADP further stimulates platelets increasing the overall activation cascade; it also modifies the platelet membrane in such a way as to allow fibrinogen to adhere to two platelet surface glycoproteins, GPIIb and GPIIIa, resulting in fibrinogen-induced platelet aggregation (25).

1.1.2.12 Platelet ProcoagulantActivity:

Once platelet aggregates are formed, there is a tendency for the fibrin threads to be laid on them to form a clot. This process is facilitated by the platelets, possibly via more than one mechanism (27).

Phospholipids on the platelet membrane support the intrinsic pathway of coagulation, which results in the formation of thrombin from prothrombin by activated factor X. The platelet surface also prevents active coagulation factors from inactivation by their natural inhibitors. Considering platelet release reactions, platelet factor 4 looks to possess anti heparin activity, and fibrinogen that is released from platelet granules may potentially contribute further to the formation of the thrombus. Also, P-selectin expression could result in platelet–leukocyte interaction making fibrin deposition by the leukocytes to form thrombus (27). In summary the procoagualt activity of platelet called by platelets; the coagulation process is a complex series of enzymatic reactions involving the proteolytic activation of circulating coagulation factors (zymogens) and activity of cofactors (V, VIII), leading to production of thrombin which converts soluble plasma fibrinogen into fibrin. The fibrin enmeshes the platelet plug, forming a stable thrombus which prevents further blood loss from the damaged vessel (27).

1.1.3 Platelet Indices:

Circulating platelets are very different in size, metabolism, and functional activity. Automated counters provide platelet counts and generate the MPV

and a measure of their size variability (PDW). The great dispersion of platelet volumes (log-normal distribution) depends on the process of platelet production, by fragmentation of cytoplasm of megakaryocytes and pro platelet formation (28). Several investigators have used a series of platelet indices measured by hematology analyzersgiven the fact that platelet activation causes morphologic changes of platelets. Recently, platelet indices; MPV and PDW have been investigated as prospective platelet activation markers (29). The present effort for finding simple and widely used platelet activation indices focused on the fact that platelet activation causes morphologic changes of platelets, including both the spherical shape and pseudopodia formation. Platelets with increased number and size of pseudopodia differ in size, possibly affecting PDW. MPV and especially PDW increase during platelet activation, as depicted by automated hematology analyzers. PDW seems to be a more specific indicator of platelet activation than MPV, since it was not elevated during single platelet distention caused by platelet swelling. The combined use of MPV and PDW could predict activation of coagulation more efficiently (30).

1.1.3.1 Mean Platelet Volume (MPV):

1.1.3.1.1 Difinition:

The mean platelet volume is an indication of platelet size. Normal MPV ranges are approximately 7 to 11 fl (31).

1.1.3.1.2 Clinical Value of MPV:

Thromboemolic diseases are among the major cause of mortality in developed countries. Early diagnosis of progressive activation of coagulation can help manage these diseases successfully. A significant list of reliable markers have been investigated recently, concerning activation of coagulation, such as prothrombin fragment, thrombin-antithrombin complex (TAT), and platelet activation, such as β-thromboglobulin (β-TG) or soluble platelet P-selectin1. However, laboratory measurement of these indices is laborious and

expensive. Additionally, the above mentioned indices cannot be included in routine laboratory tests (30).The MPV can be an indication of platelet turnover because younger platelets tend to be larger. A spectrum of platelet sizes is seen in patients with rapid turnover (31).

The Largest platelets are more reactive and release a greater quantity of thrombogenic factors as they contain more dense granules and produce more thromboxane A2.Increased MPV has been associated with greater in vitro aggregation in response to ADP and collagen. Platelet volume seems to be correlated with megakaryocyte ploidy as, the increase of MPV in conditions with increased platelet turnover is probably mediated by several cytokines (interleukins 6 and 11 and thrombopoietin) that affect megakaryocyte ploidy and result in the production of larger and more reactive platelets (26). Several experimental and clinical studies have demonstrated that platelet size and function correlate since large platelets are hemostatically more reactive than platelets of normal size. Elevated MPV levels have been identified as an independent risk factor for thrombotic diseases (32).

1.1.3.1.3 Causes of raised MPV:

MPV is significantly increased in:

1. Idiopathic thrombocytopenic purpura.
2. Bernard- Soulier disease.
3. May-Hegglin anomaly.

1.1.3.1.4 Causes of low MPV:

MPV is significantly decreased in:

1. Aplastic anemia.
2. Wiskott-Aldrich syndrome.
3. Thrombocytopenia-absent radii (TAR).
4. Storage Pool disease (26).

1.1.3.1.5 Influences of drugs on MPV:

Little is known about effects of various drugs on platelet size. Previous in vitro studies found no effect of aspirin on platelet size. Clinical data on a possible association of MPV with various platelet inhibitors in patients do not exist (33).

1.1.3.2 Platelet distribution width (PDW):

The PDW can also be useful in differentiating reactive thrombocytosis from the essential type, especially when it is combined mathematically with the MPV and platelet count to obtain a discriminate function (33).PDW is also potentially useful marker for the early diagnosis of thromboembolic diseases and an increase in PDW due to platelet activation, resulting from platelet swelling and pseudopodia formation was hypothesized, however PDW is reported to be a more specific marker of platelet activation than MPV, since it does not increase during simple platelet swelling (30).

1.2 Previous Studies:

Univesidade federal de juiz de for a ,minas gerais , brasil , a study conducted to evaluate platelet parameters in patients with type 2 DM from February 2013 to January 2014, the study included 100 patient wih T2DM and 100 non –diabetics as control ,results: they observed increase in MPV (8.69-1.288 flvs. 8.27-1.244fl (p=0.018)) , and in PDW(17.8-1.06 fl vs. 17.5-0.87 fl (p=0.039)) in the diabetics and control respectively (34).

(Papanas et al., 2004) investigated MPV in type 2 DM and evaluated its associations to diabetic complications. They found that MPV was significantly higher (P = 0.01) in diabetics (14.2 +/- 2.2 fl) than in non-diabetics (7.1 +/- 1.2 fl). Among diabetic they found that no association was found between MPV and age, gender, duration of diabetes and HbA1c(35).

Sharpe and Trinick, (1993) measured MPV in patients with diabetes mellitus, compared with MPV in non-diabetic control subjects. Mean MPV was significantly increased in the diabetic subjects (8.9 +/- 0.07 fL, mean +/-

SEM) compared with non-diabetic subjects (8.0 +/- 0.05) ($p < 0.001$). They reported that since platelet size is a determinant of platelet function, with larger platelets being more reactive per unit volume, they believe platelets may play a part in the micro- and macro-vascular complications of diabetes mellitus(36).

In Nigeria conducted an unmatched case-control study involving 200 participants consisting of 100 diabetics and 100 non-diabetic controls. Four and half milliliters of blood were collected from diabetics and non-diabetic controls into EDTA anticoagulant tubes. Full blood count was performed using the Sysmex KN-21N, (manufactured by Sysmex corporation Kobe, Japan) a three- part auto analyzer able to run 19 parameters per sample including platelet counts and mean platelet volume. The mean fasting blood sugar for the diabetics was

147.85±72.54 mg/dl and the controls 95.20±30.10 mg/dl. The mean platelet count for the diabetics was 235.29±76.81 X 109/L and controls, 211.32±66.44 X 109/L. The mean platelet volume, for the diabetics was 8.69±0.67 fl and the controls, 8.91±0.80 fl. There was a statistically significant difference in platelet counts of diabetics and healthy controls ($p=0.038$) while none existed between the mean platelet volume in diabetics and healthy controls ($p = 0.593$). This study revealed a higher mean platelet count for diabetics on treatment than for non-diabetic controls while mean platelet volume was lower in cases than controls. However, both parameters in diabetics on treatment were within the normal reference range for healthy individuals(37).

A study done in Sudan in soba university hospital from March to May 2011 to study platelet indices in type2 diabetic patients. a total of 40 Sudanese patients with type 2 diabetes mellitus and 10 non diabetic individuals as control were enrolled in this study , two and half ml of venous blood was collected from all individuals in EDTA anticoagulant. A blood cell counter sysmex KX-21 was used to measure PI within two hours of sample collection.

The result of this study all platelet indices were significantly raised in diabetic patients, mean MPV 9.97 FL (P=0.001) and mean PDW 12 .54 FL (P=0.010) compared with non-diabetic individuals, mean MPV 9.1 FL, and mean PDW 11.89 FL(38).

1.3 Rationale :

Type 2 Diabetes Mellitus is global public health problem that threaten the economies of all nations, particularly developing countries . microvascular and macrovascular complications are major causes of mortality in Persons with Diabetes. Platelets hyper activation in type2 DM is believed to playan important role in the development of these complication .recent advances in diagnostics have established MPV and PDW are considered as platelet activation markers. There is a limited publish data regarding the platelet indices in patients with type 2 DM in Sudan .Therefore this study was conducted to assessment of platelet indices in Sudanese patients with type 2DM .the results may have clinical applications in risk stratification and targeting prevention and management therapy for patients with type 2 Diabetes Mellitus.

1.4. Objectives:

1.4.1. General Objective:

To evaluate of platelet indices in patients with type 2 Diabetes Mellitus "T2DM"in Atbara City 2018.

1.4.2.Specific Objectives:

1- To estimate of platelet indices (MPV and PDW) in patient with “T2 DM” in Atbara city 2018.

2-To estimate platelet indices in healthy population in Atbara city 2018.

3- To compare the result of platelet indices between diabetic patients and normal control group.

2. Materials and Methods

2.1 Study Design:

Cross sectional study.

2.2 Study Area and Setting:

The study was conducted at Atbara hospital which located in Atbara Town in northern Sudan during the period between March to July 2018.Atbara is a town in northern Sudan between a river Nile and Atbara River .its main town in river Nile.

2.3 Study Population:

50 Sudanese patients with type 2 diabetes mellitus diagnosed according to (WHO) criteria , included both sexes , their ages ranged between (30 – 70) years and 50 healthy individuals as a control group.

2.4 Ethical Consideration:

The individuals included in the study were notified well about the objective and the need of this study and they accept to give blood samples before the start of the collection process.

2.5 Sample Size:

Sample size was 50 diabetic patient and50 was healthy control group.

2.6 Inclusion Criteria for the Cases:

Non-insulin dependent diabetes mellitus patient on treatment attending the diabetes clinic.

2.7 Exclusion Criteria for the Cases:

Severely complicated diabetic patient and insulin dependent diabetes and patient with medications that affect platelet activation.

2.8 Data Collection:

The primary data was collected by a standard questionnaire and the secondary data was analyzed.

2.9 Sample Collection:

3ml of Venous blood was collected using sterile disposable plastic syringe

The vein puncture area was cleaned with 70% ethanol and blood was added to EDTA anticoagulant .the specimen was labeled with subject's age, sex and identification number.

2.10 Tests Applied:

2.10.1 Measurement of platelet indices and platelet count:

MPV and platelet count were measured using a Sysmex KX N21 autoanalyzer that uses aperture-impedance technology to size platelets on the red blood cell/platelet channel that produces the following parameters: PLT (109/L), MPV (fL), and PDW [calculated as (σ × 100) (fL)/MPV (fL) after log transformation of the MPV]. In addition to this, cells are hydrodynamically focused through a small aperture, and a voltage pulse is generated that is proportional in size to the volume of the cell. Mobile "auto discriminators" distinguishes between machine noise at the lower end and red blood cells at the upper end of each individual platelet volume distribution. MPV is calculated by the following formula: MPV (fL) =platelet crit (Pct) (%) x1000÷Plt (x103/μL), where platelet is the platelet count and is the number of particles between the upper andlower discriminators, Pct is calculated electronically from the raw histogram data.

Complete blood count including platelet indices was measured within 1 hour of collection to minimize variations due to sample aging. The complete blood count including platelet indices was performed following manufacturer instructions as follow:

The whole blood mode (WB) was selected to analyze the whole blood sample without pre-dilution. The sample number was entered before each sample. This procedure was followed:

 A well-mixed anti-coagulated sample was set to the sample probe, and the start switch was pressed till the aspirating process was finished. (Volume aspirated approx. 50mL).

 The sample was removed straight down and the sample probe was automatically cleaned.

 The aspirated sample was then automatically suspended into the different detector blocks and different parameters were measured.

 The results of parameters were then viewed on the screen and subsequently printed out.

2.10.2 Microscopic Examination of Thin Blood Film

The well spread thin blood films that were made immediately after collection was stained as follows:

- Films were left to dry.
- After drying well they were covered by diff quick three solutions:

-Slide was dipped five times, for one second each, into fixative, excess was allowed to drain after each dip.

-Slide was dipped five times, forone second each, into stain, excess was allowed to drain after each dip.

-slide was dipped five times, for one second each, into stain, excess was allowed to drain after each dip.

- The slides were rinsed in distilled water.
- The films were then wiped clean on the other side, and left to dry.
- Lastly the well –spread, stained and dried blood films were examined microscopically using X 100 objective lens. Any specimen showed

Fragment of RBCs orother blood cells or aggregated platelet was excluded.

2.11 Data Analysis:

Data was analyzed by SPSS (Statistical Package for the Social Science).

2.12 Data Presentation:

Data was presented in form of table and figures.

3. Result Description

Table (3-1) distribution of study population according to gender

	Frequency	Percent
Male	16	32.0%
Female	34	68.0%
Total	50	100.0%

Mean : 1.68

P. value : 0.067

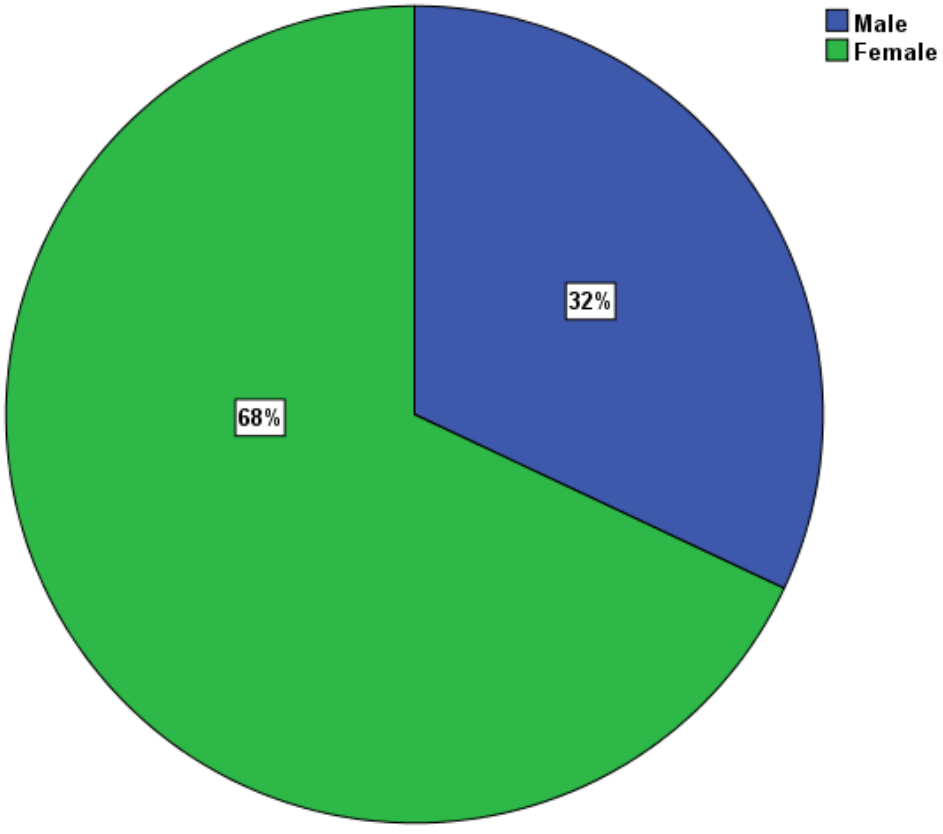


Figure (3-1) distribution of study population according to gender

Table (3-2) distribution of study population according to age group

	Frequency	Percent
30 - 40 years	1	2.0%
41 - 50 years	12	24.0%
51 - 60 years	22	44.0%
61 - 70 years	10	20.0%
> 70 years	5	10.0%
Total	50	100.0%

Mean : 3.12

P. value : 0.096

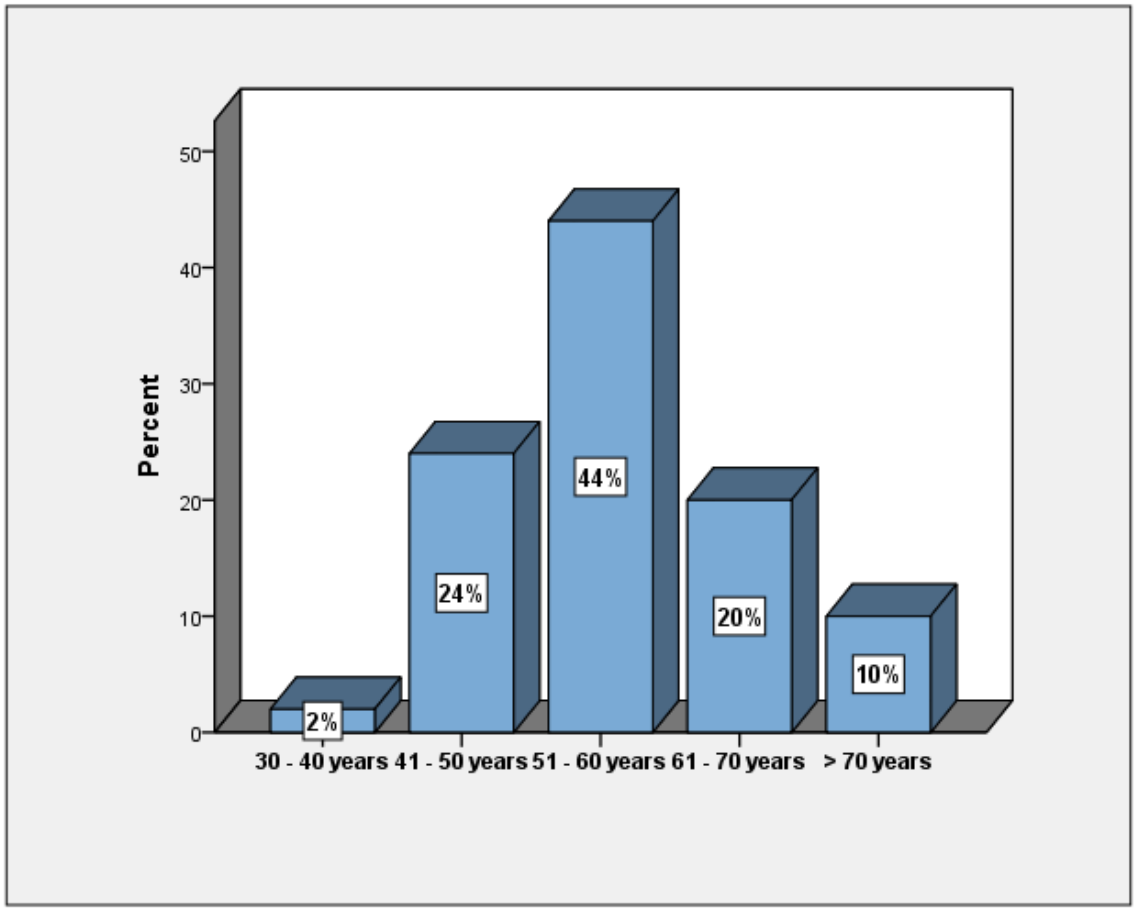


Figure (3-2) distribution of study population according to age group

Table (3-3) distribution of study population according to height

	Frequency	Percent
< 1.50 m	4	8.0%
1.50 - 1.60 m	16	32.0%
1.61 - 1.70 m	16	32.0%
1.71 - 1.80 m	9	18.0%
> 1.80 m	5	10.0%
Total	50	100.0%

Mean : 2.90

P. value : 0.015

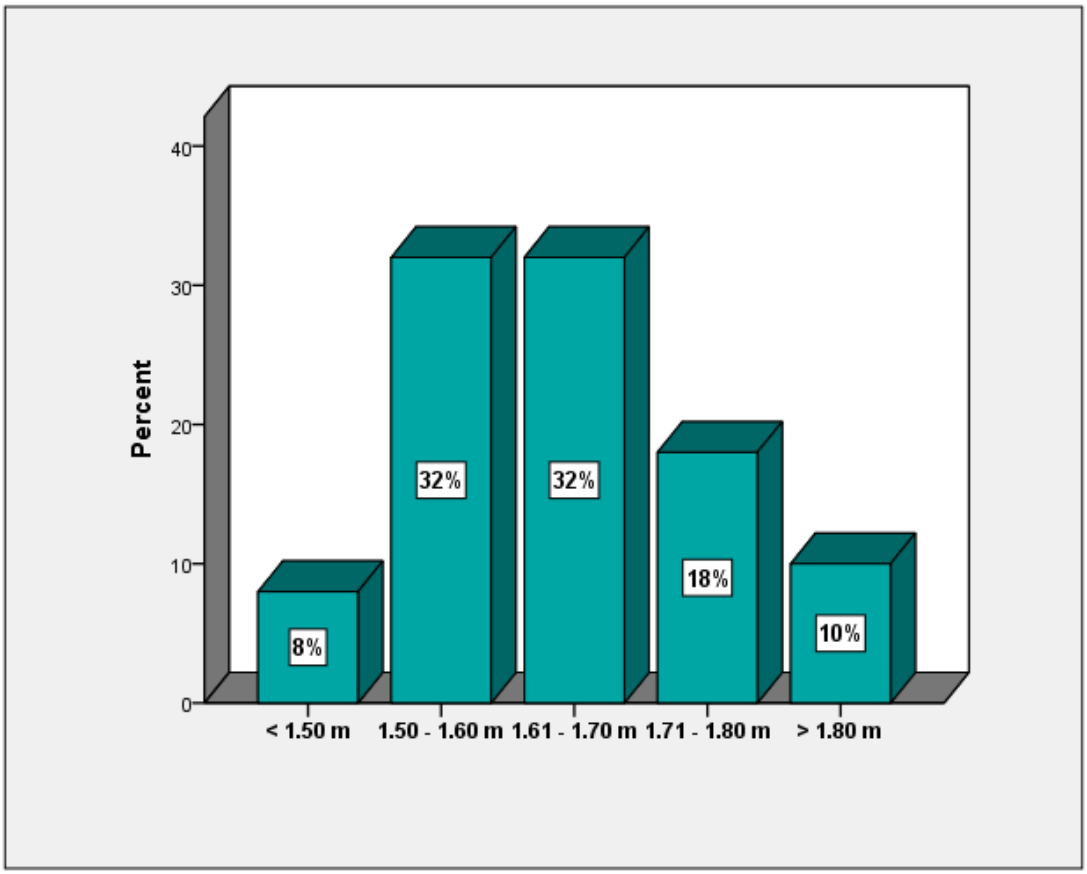


Figure (3-3) distribution of study population according to height

Table (3-4) distribution of study population according to weight

	Frequency	Percent
< 55 kg	1	2.0%
55 - 70 kg	18	36.0%
71 - 85 kg	15	30.0%
86 - 100 kg	12	24.0%
> 100 kg	4	8.0%
Total	50	100.0%

Mean : 3.00

P. value : 0.014

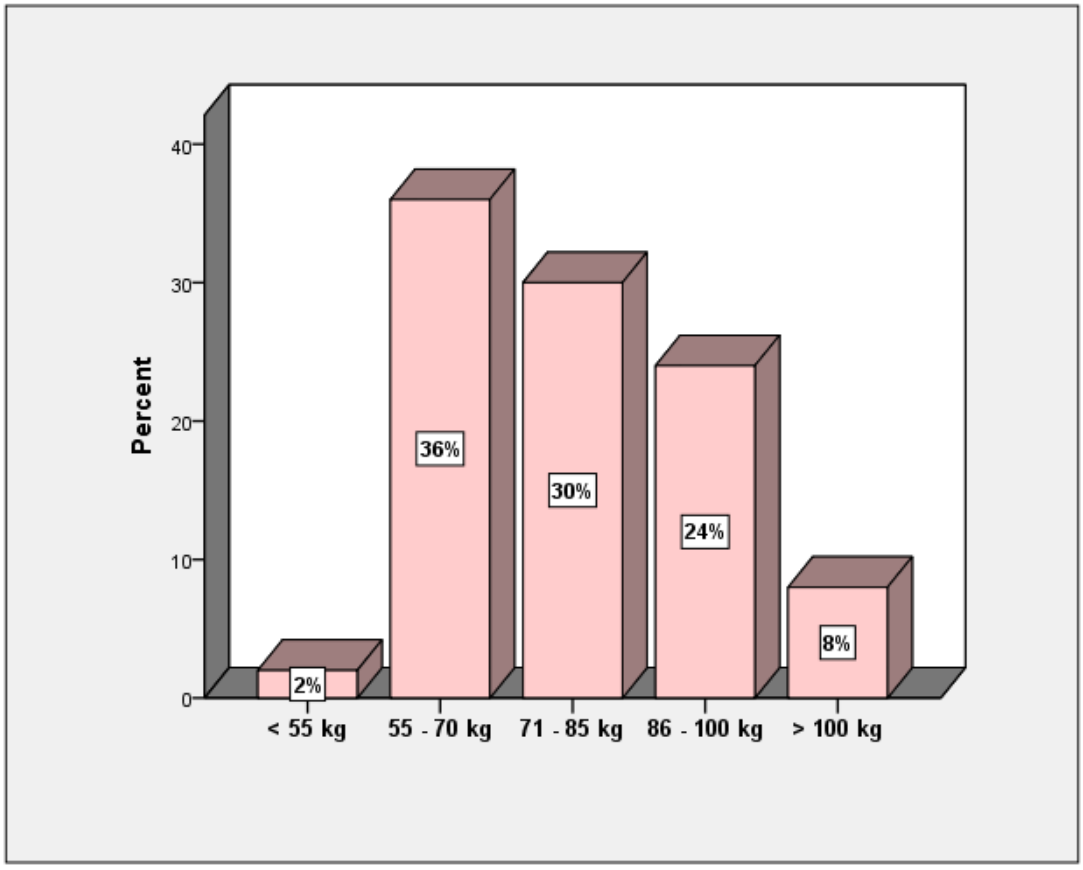


Figure (3-4) distribution of study population according to weight

Table (3-5) distribution of study population according to BMI

	Frequency	Percent
< 20	2	4.0%
20 - 30	35	70.0%
31 - 40	7	14.0%
41 - 50	5	10.0%
> 50	1	2.0%
Total	50	100.0%

Mean : 3.22

P. value : 0.018

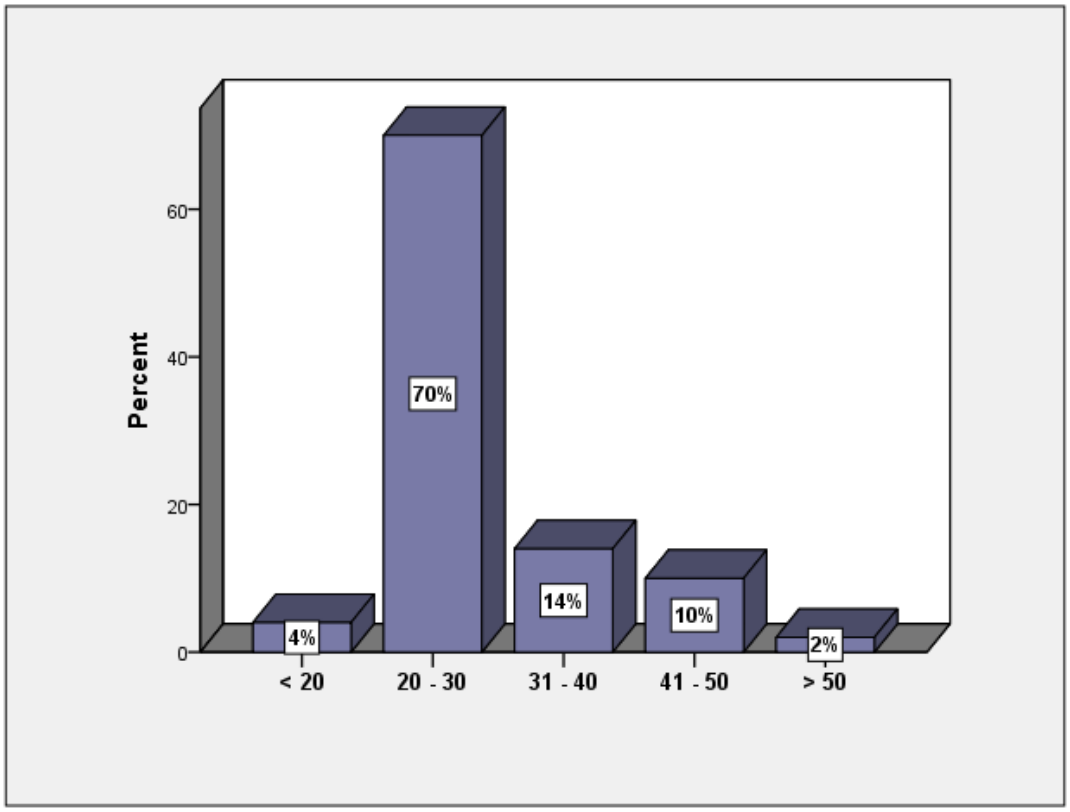


Figure (3-5) distribution of study population according to BMI

Table (3-6) distribution of study population according to duration of disease

	Frequency	Percent
< 1 year	4	8.0%
1 - 5 years	12	24.0%
6 - 10 years	15	30.0%
11 - 15 years	7	14.0%
> 15 years	12	24.0%
Total	50	100.0%

Mean : 1.44

P. value : 0.007

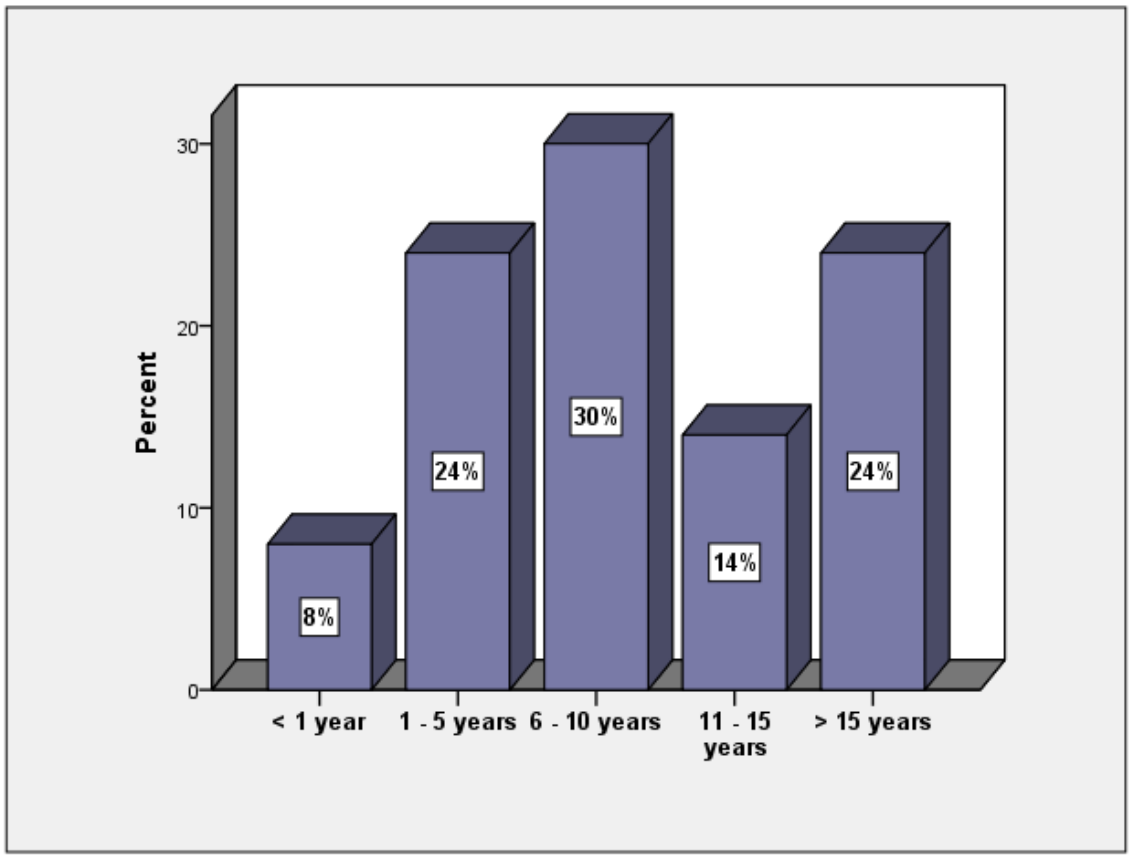


Figure (3-6) distribution of study population according to duration of disease

Table (3-7) distribution of study population according to family history of disease

	Frequency	Percent
Yes	28	56.0%
No	22	44.0%
Total	50	100.0%

Mean : 1.74

P. value : 0.011

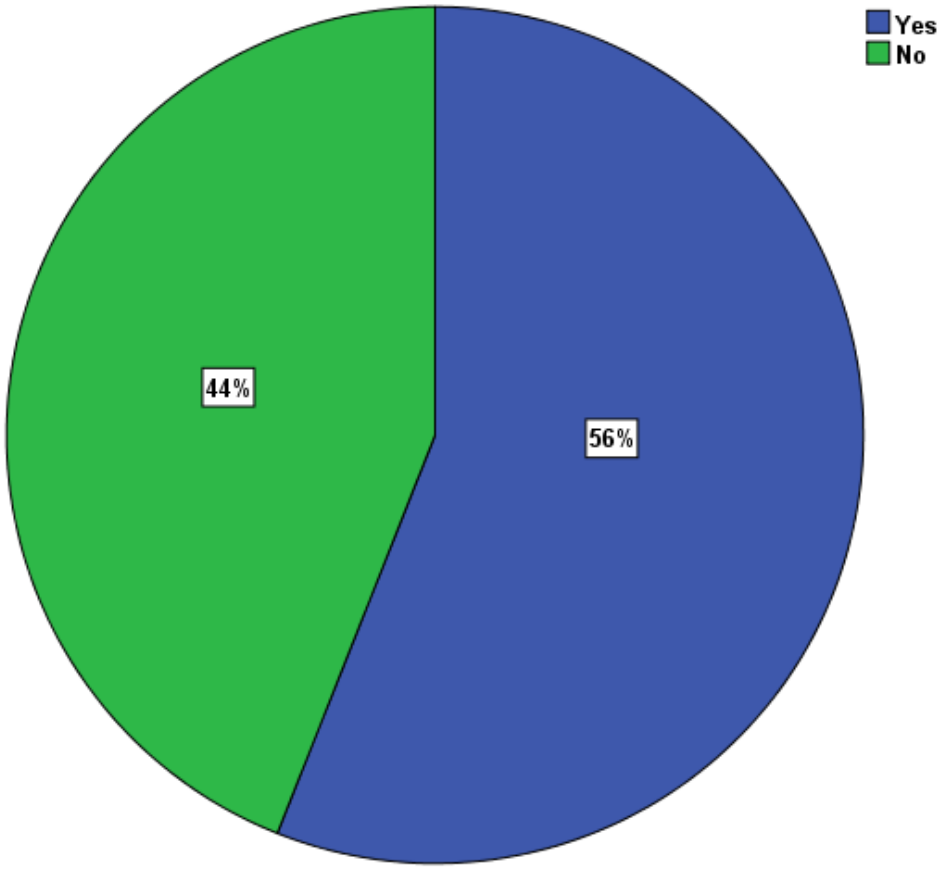


Figure (3-7) distribution of study population according to family history of disease

Table (3-8) distribution of study population according to type of treatment

	Frequency	Percent
Insulin	24	48.0
Drugs	15	30.0
No treatment	11	22.0
Total	50	100.0

Mean : 1.90

P. value : 0.025

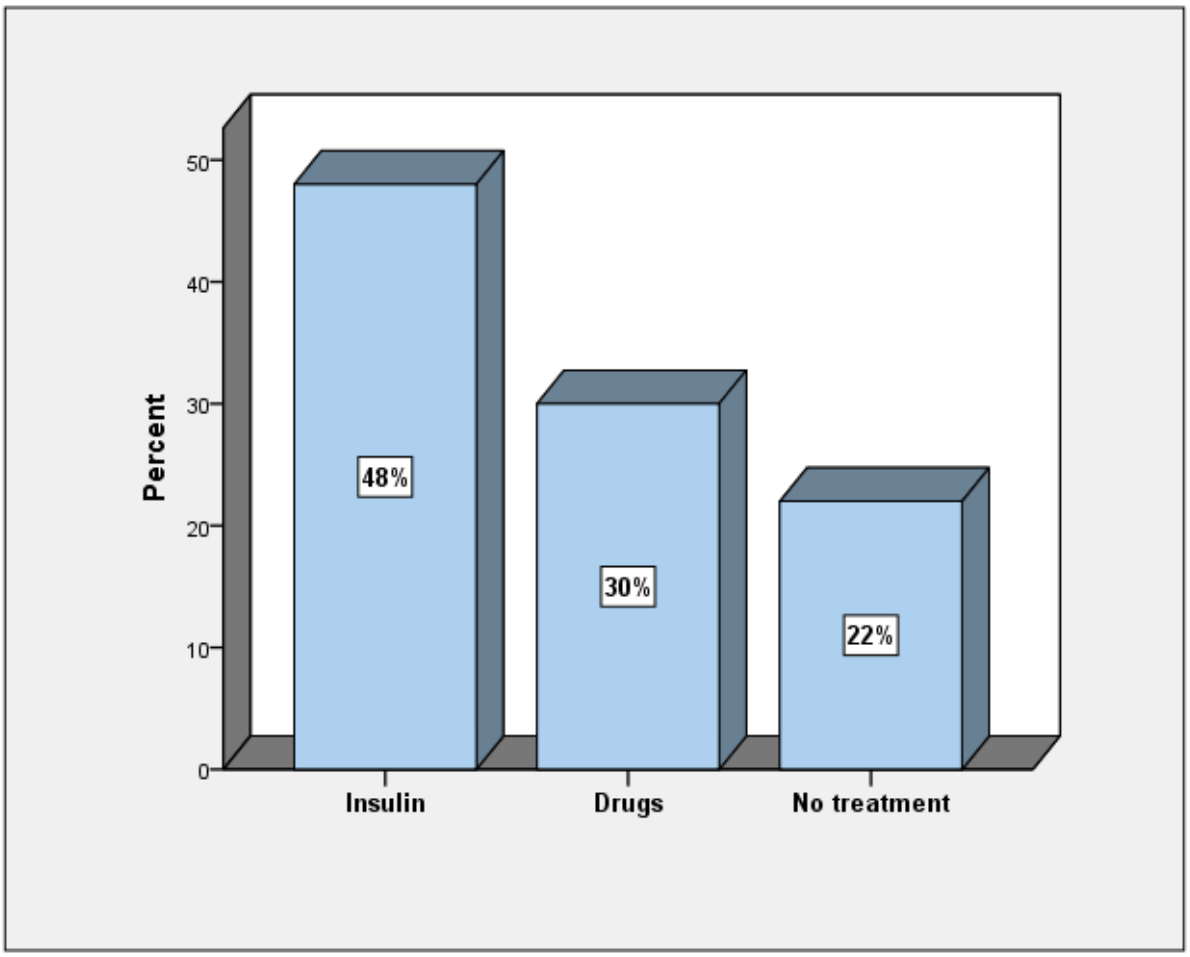


Figure (3-8) distribution of study population according to type of treatment

Table (3-9) distribution of study population according to complication

	Frequency	Percent
No complication	38	76.0%
Gas gangrene	5	10.0%
Ischemia	1	2.0%
Renal failure	1	2.0%
Glycoma	3	6.0%
Hypertension + Gas gangrene	1	2.0%
Hypertension + Glycoma	1	2.0%
Total	50	100.0%

Mean : 1.70

P. value : 0.006

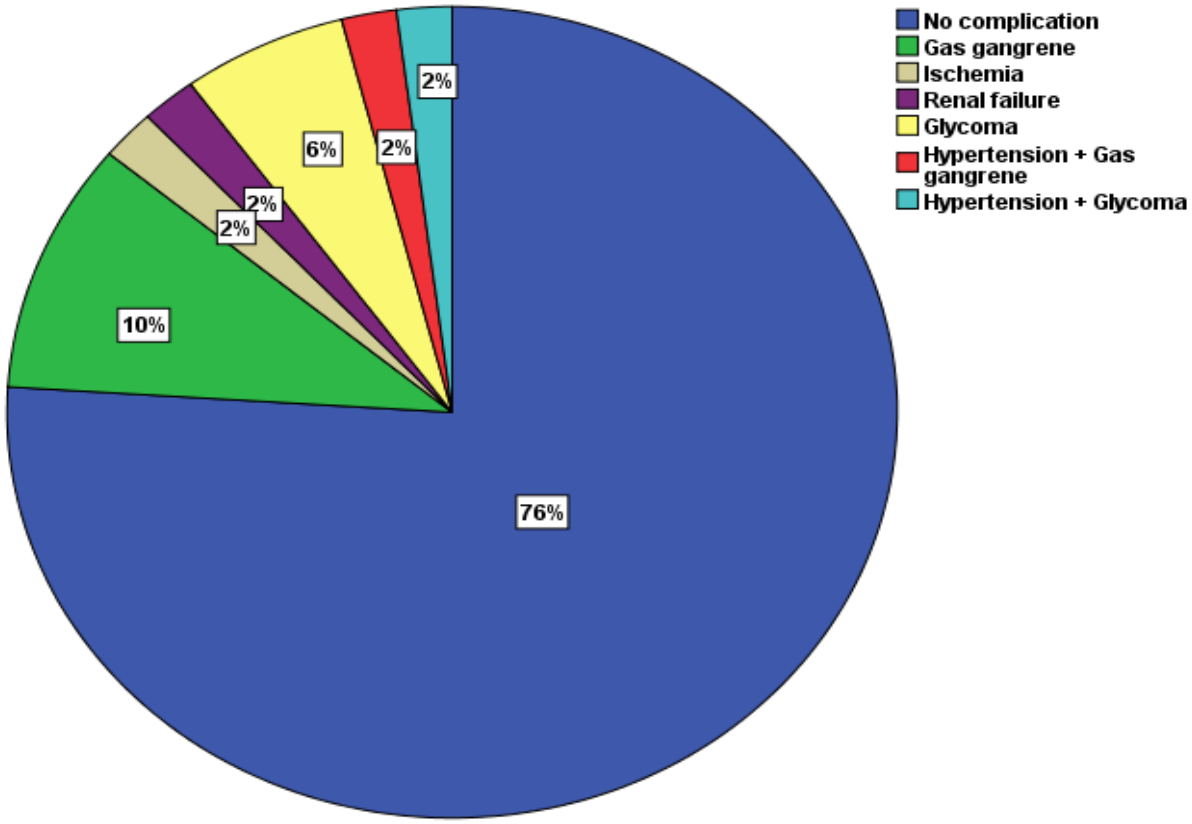


Figure (3-9) distribution of study population according to complication

Table (3-10) distribution of study population according to wounds

	Frequency	Percent
Found	15	30.0%
Not found	35	70.0%
Total	50	100.0%

Mean : 1.16

P. value : 0.005

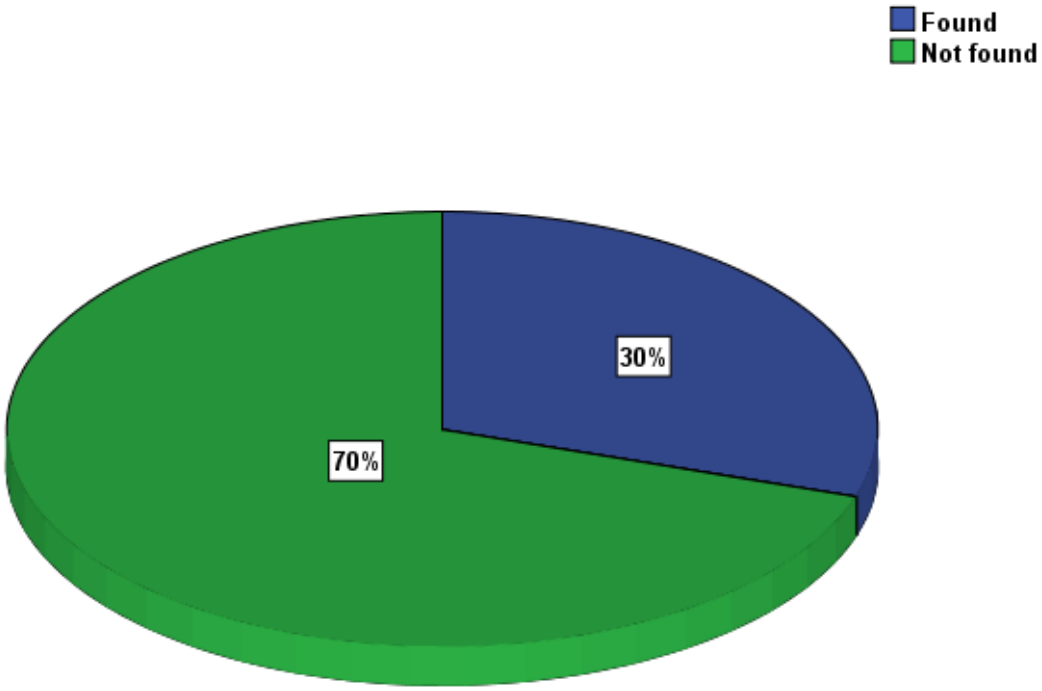


Figure (3-10) distribution of study population according to wounds

Table (3-11) distribution of study population according to wounds healing

	Frequency	Percent
Fast	42	84.0%
Slow	8	16.0%
Total	50	100.0%

Mean : 1.38

P. value : 0.013

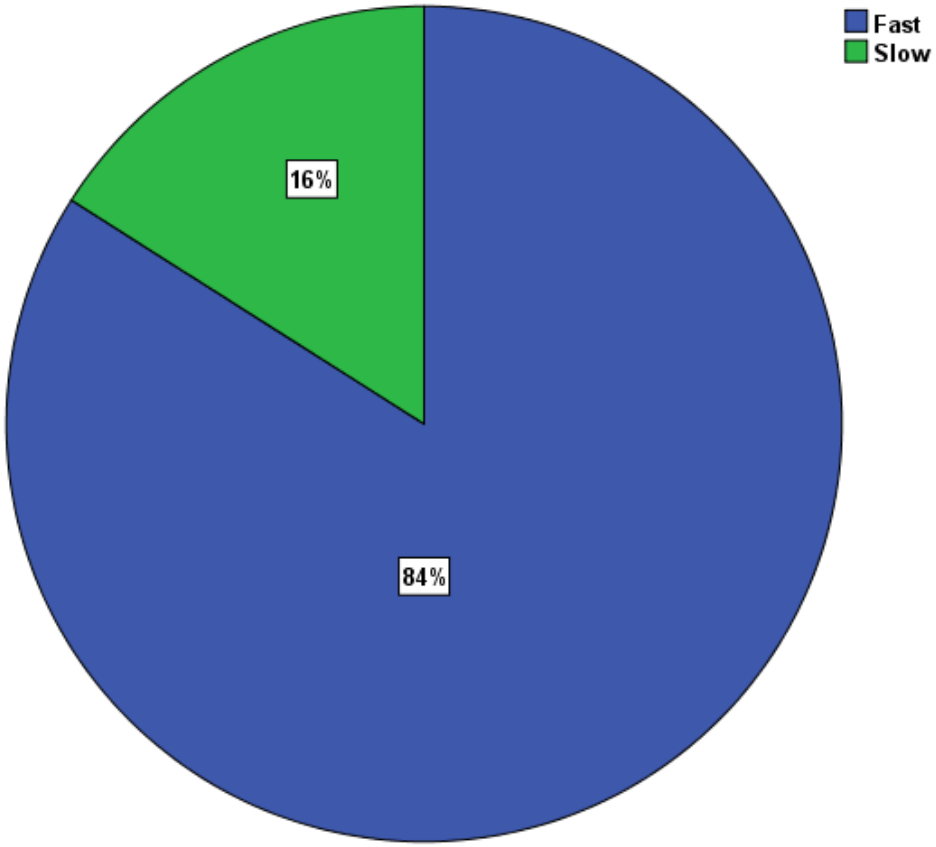


Figure (3-11) distribution of study population according to wounds healing

Table (3-12) distribution of study population according to other disease

	Frequency	Percent
No other disease	39	78.0%
Hypertension	8	16.0%
Cholesterol	1	2.0%
Hypertension + Arthritis	1	2.0%
Hypertension + Cholesterol	1	2.0%
Total	50	100.0%

Mean : 2.98

P. value : 0.019

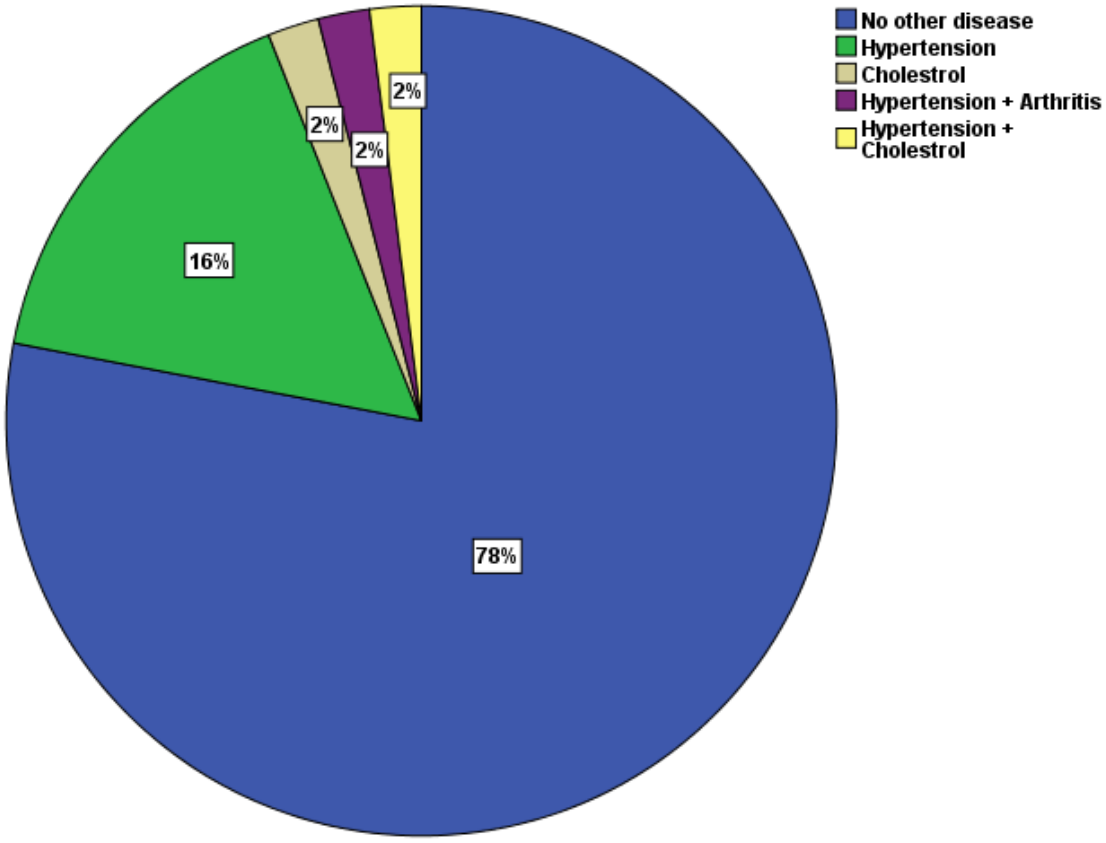


Figure (3-12) distribution of study population according to other disease

Table (3-13) distribution of study population according to platelets count

	Frequency	Percent
< 200	11	22.0%
200 - 240	7	14.0%
241 - 280	12	24.0%
281 - 320	12	24.0%
> 320	8	16.0%
Total	50	100.0%

Mean : 3.30

P. value : 0.018

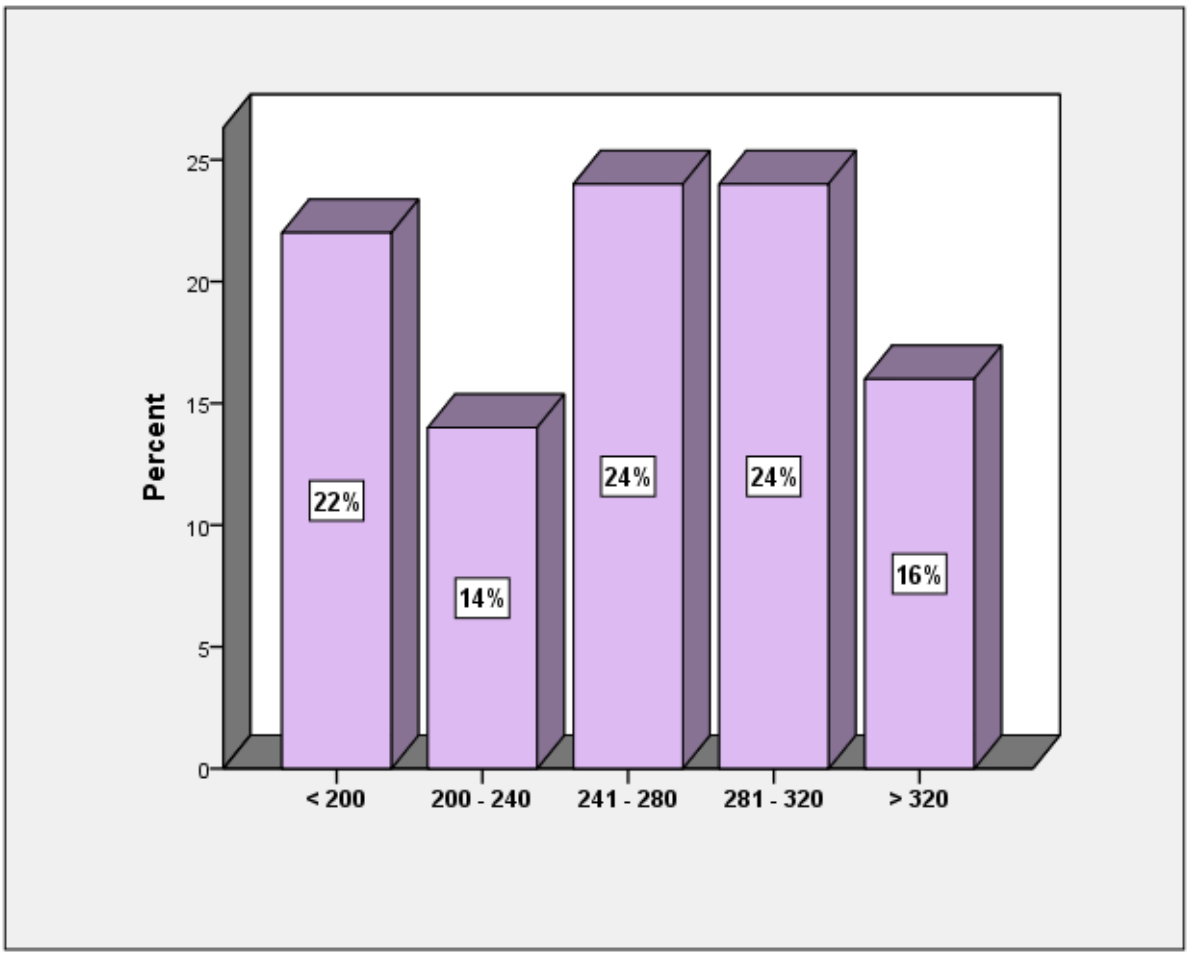


Figure (3-13) distribution of study population according to platelets count

Table (3-14) distribution of study population according to main platelets volumes

	Frequency	Percent
< 10	5	10.0
10 - 10.5	7	14.0
10.6 - 11.0	11	22.0
11.1 - 11.5	12	24.0
> 11.5	15	30.0
Total	50	100.0

Mean : 3.76

P. value : 0.017

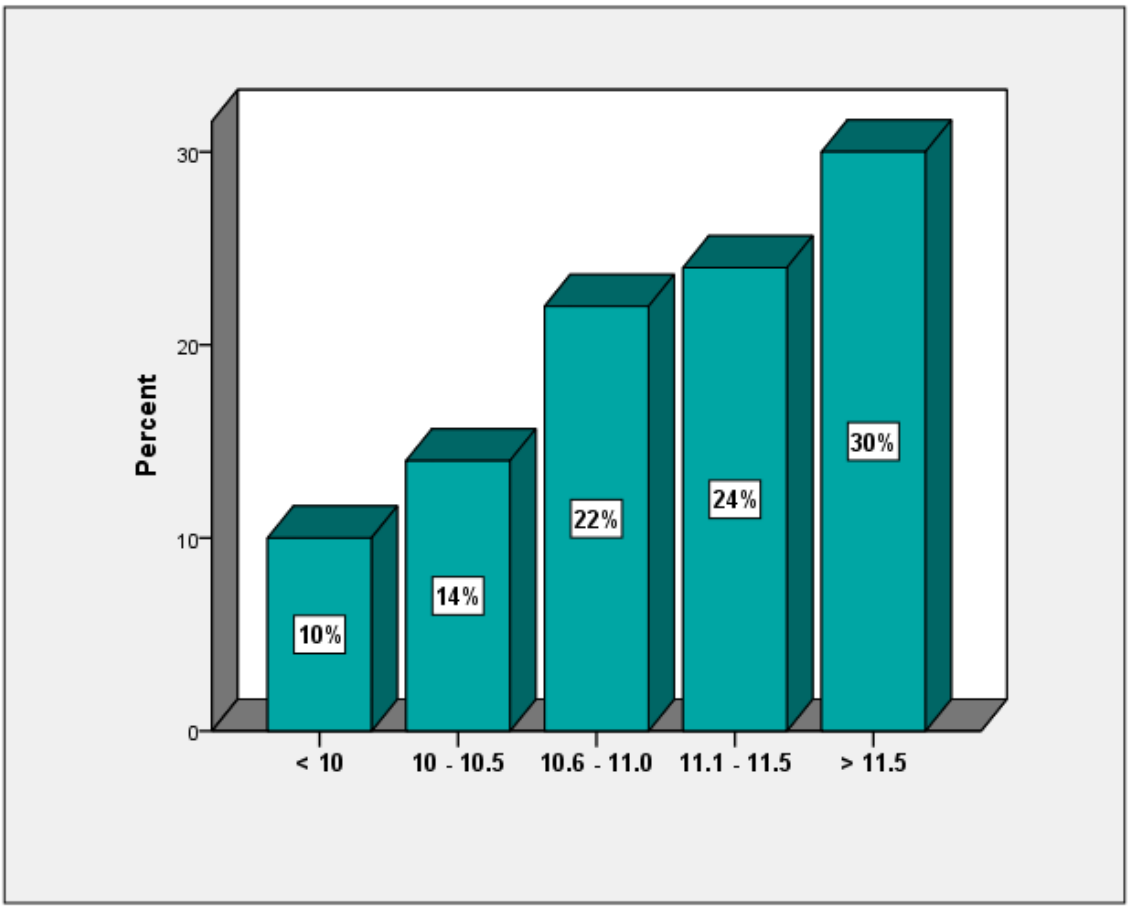


Figure (3-14) distribution of study population according to main platelets volumes

Table (3-15) distribution of study population according to platelets distribution width

	Frequency	Percent
< 12	3	6.0
12 - 13	4	8.0
13.1 - 14	13	26.0
14.1 - 15	12	24.0
> 15	18	36.0
Total	50	100.0

Mean : 2.38

P. value : 0.016

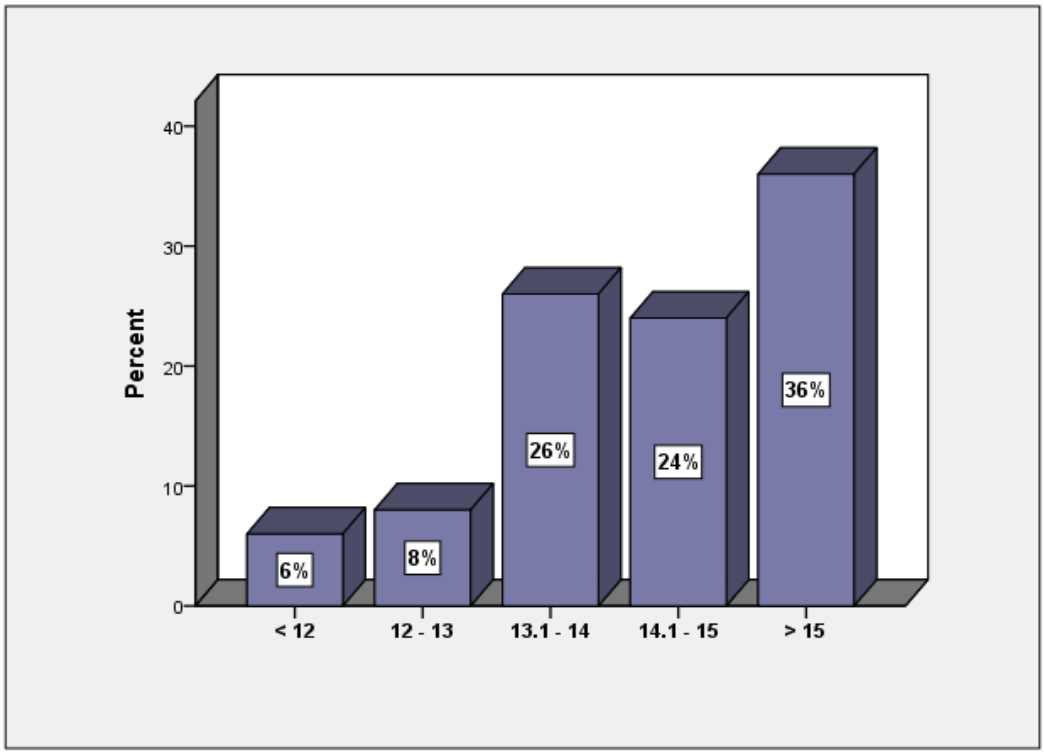


Figure (3-15) distribution of study population according to platelets distribution width

Table (3-16) distribution of study population according to fasting sugar level

	Frequency	Percent
< 150	15	30.0
150 – 200	11	22.0
201 – 250	17	34.0
251 – 300	4	8.0
> 300	3	6.0
Total	50	100.0

Mean : 3.52

P. value : 0.019

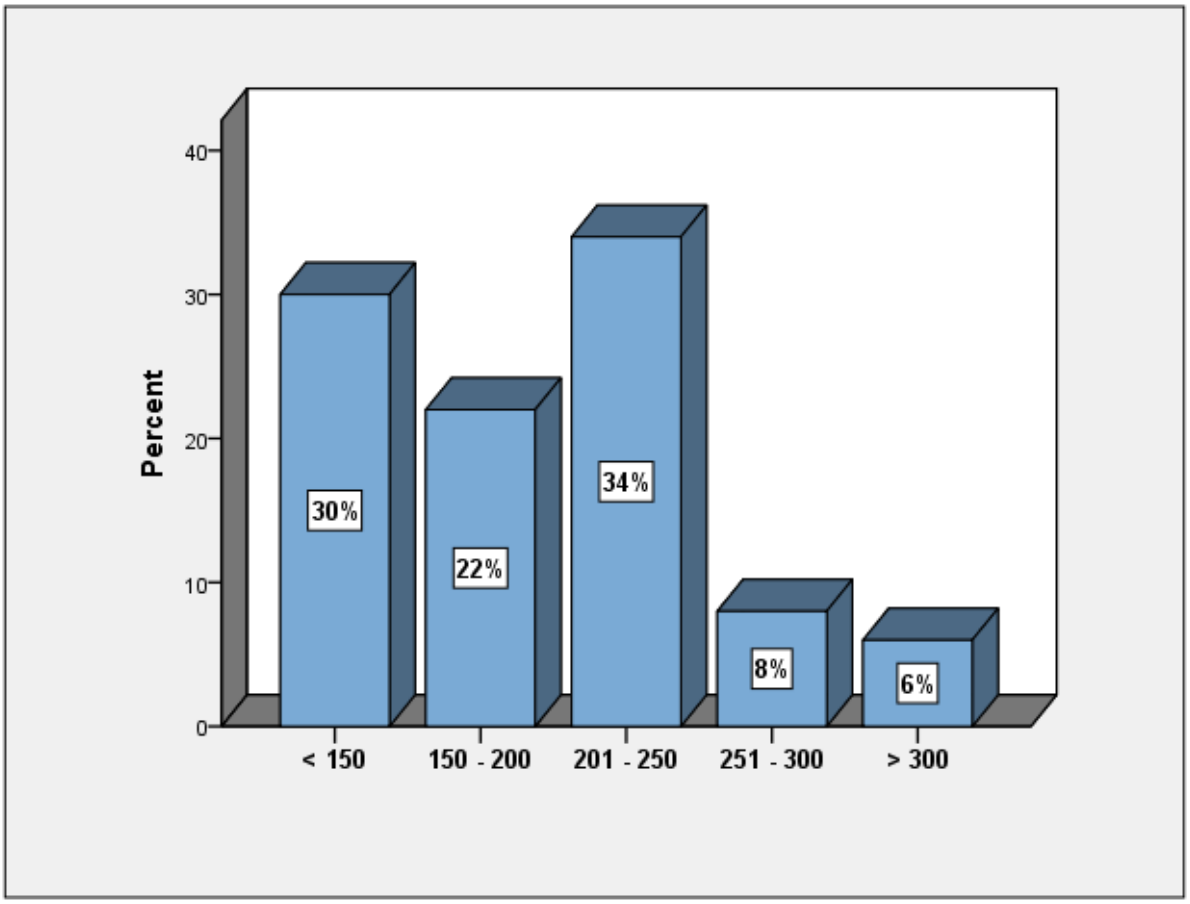


Figure (3-16) distribution of study population according to fasting sugar level

Table (3-17) distribution of study population according to sugar level after 2 hours

	Frequency	Percent
< 150	7	14.0%
150 – 200	5	10.0%
200 – 250	9	18.0%
251 – 300	13	26.0%
> 300	16	32.0%
Total	50	100.0%

Mean : 2.36

P. value : 0.011

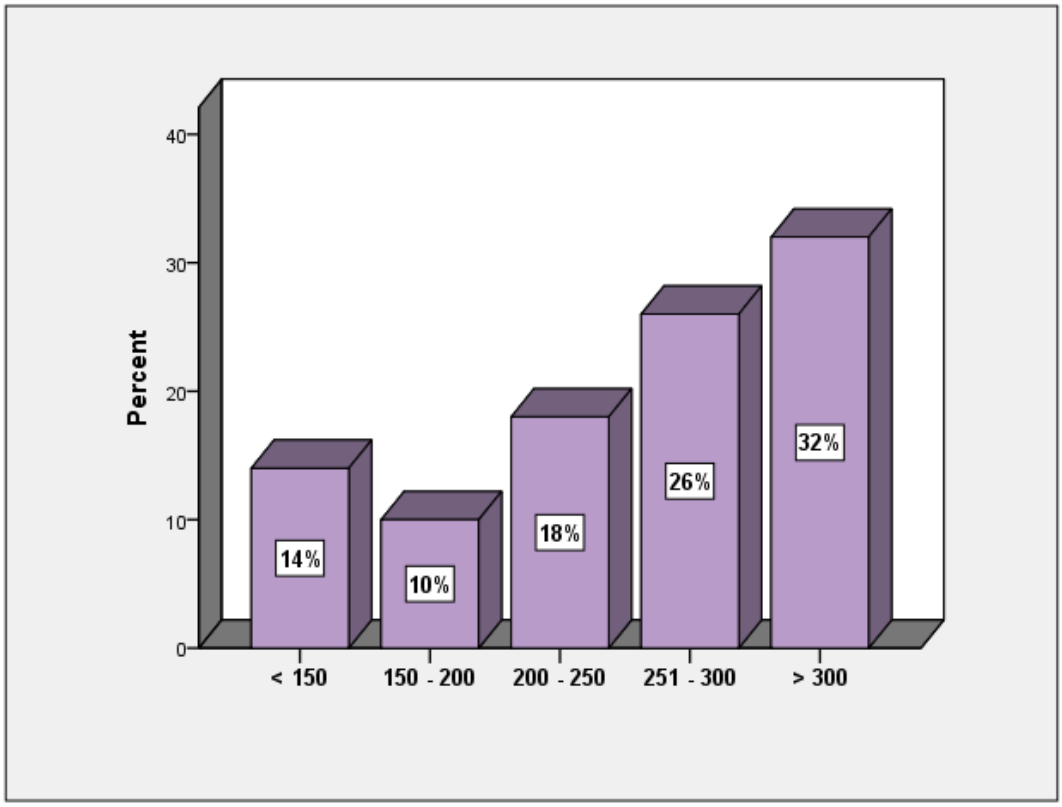


Figure (3-17) distribution of study population according to sugar level after 2 hours

Table (3-18) Crosstabulation between age of patients and control

Chi-Square Tests

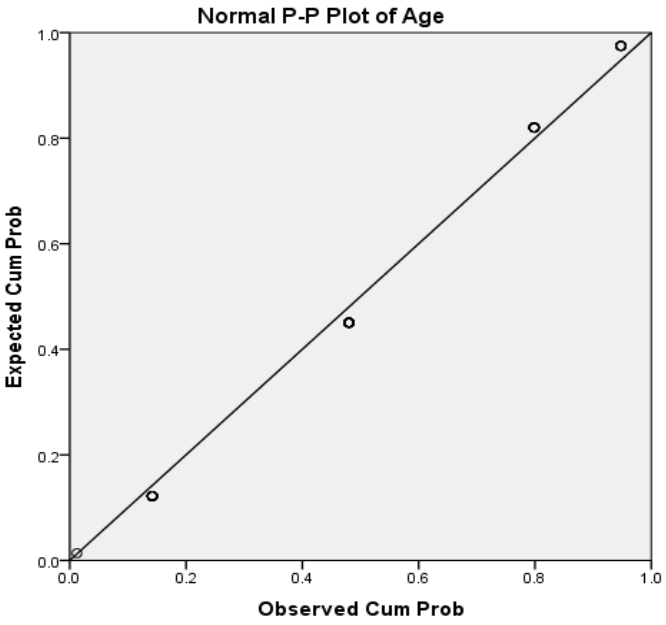
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	15.871[a]	12	.197
Likelihood Ratio	18.387	12	.104
Linear-by-Linear Association	.455	1	.500
N of Valid Cases	50		

Symmetric Measures

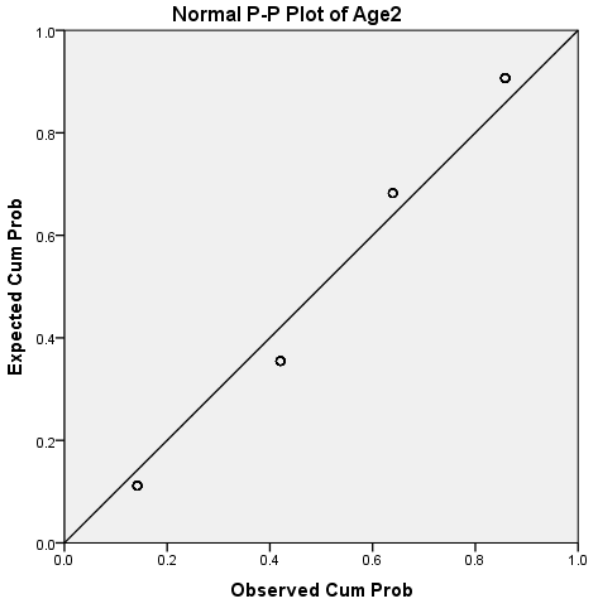
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Nominal by Nominal	Phi	.563			.197
	Cramer's V	.325			.197
Interval by Interval	Pearson's R	.096	.132	.671	.506[c]
Ordinal by Ordinal	Spearman Correlation	.070	.134	.485	.630[c]
N of Valid Cases		50			

Mean : 2.44

P. value : 0.016



Patients age



Control age

Table (3-19) Crosstabulation between body mass index of patients and control

Chi-Square Tests

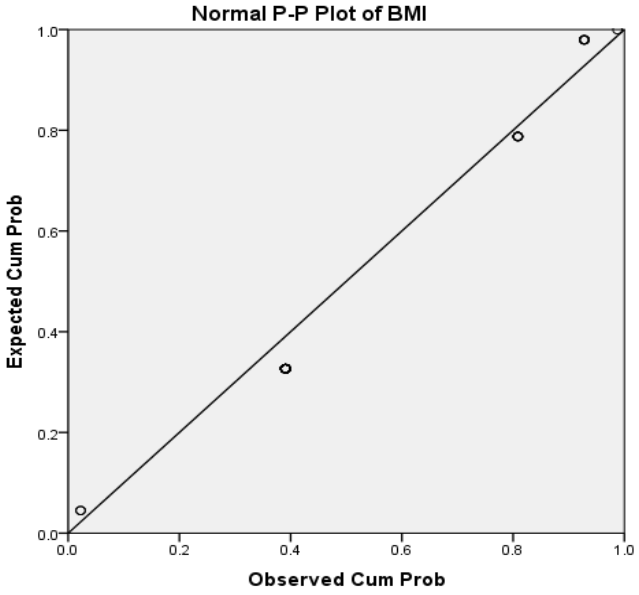
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	10.402[a]	16	.845
Likelihood Ratio	11.743	16	.761
Linear-by-Linear Association	.004	1	.947
N of Valid Cases	50		

Symmetric Measures

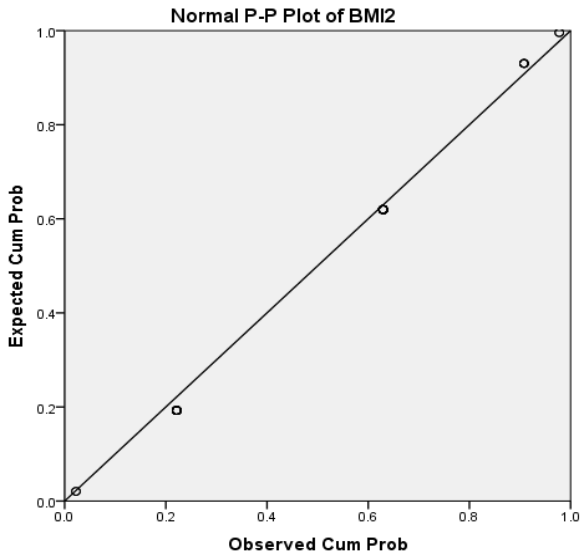
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Nominal by Nominal	Phi	.456			.845
	Cramer's V	.228			.845
Interval by Interval	Pearson's R	-.010-	.124	-.066-	.948[c]
Ordinal by Ordinal	Spearman Correlation	.033	.140	.226	.822[c]
N of Valid Cases		50			

Mean : 2.74

P. value : 0.012



Patients BMI



Control BMI

Table (3-20) Crosstabulation between platelets count of patients and control

Chi-Square Tests

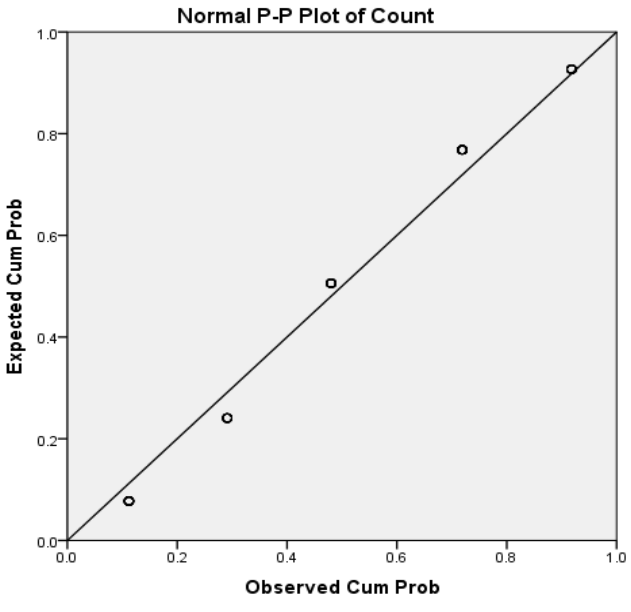
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	14.523[a]	16	.560
Likelihood Ratio	19.621	16	.238
Linear-by-Linear Association	.004	1	.951
N of Valid Cases	50		

Symmetric Measures

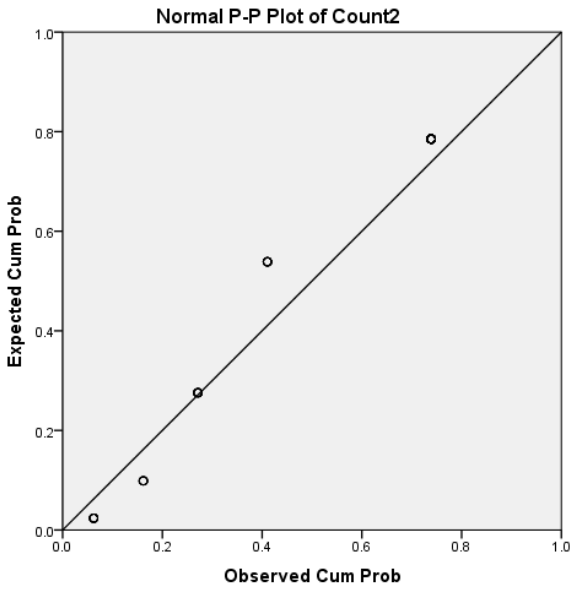
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Nominal by Nominal	Phi	.539			.560
	Cramer's V	.269			.560
Interval by Interval	Pearson's R	.009	.135	.061	.952[c]
Ordinal by Ordinal	Spearman Correlation	-.009-	.139	-.061-	.952[c]
N of Valid Cases		50			

Mean : 3.86

P. value : 0.020



Patients count



Control count

Table (3-21) Crosstabulation between main platelets volume of patients and control

Chi-Square Tests

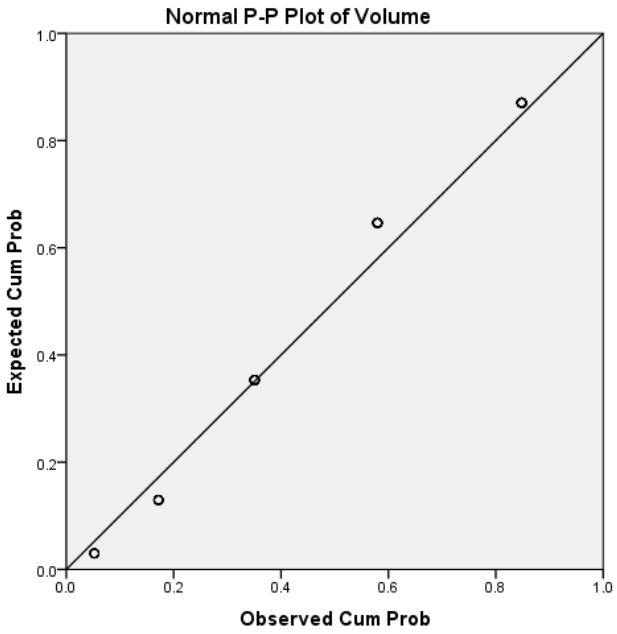
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	4.861[a]	4	.302
Likelihood Ratio	5.014	4	.286
Linear-by-Linear Association	2.655	1	.103
N of Valid Cases	50		

Symmetric Measures

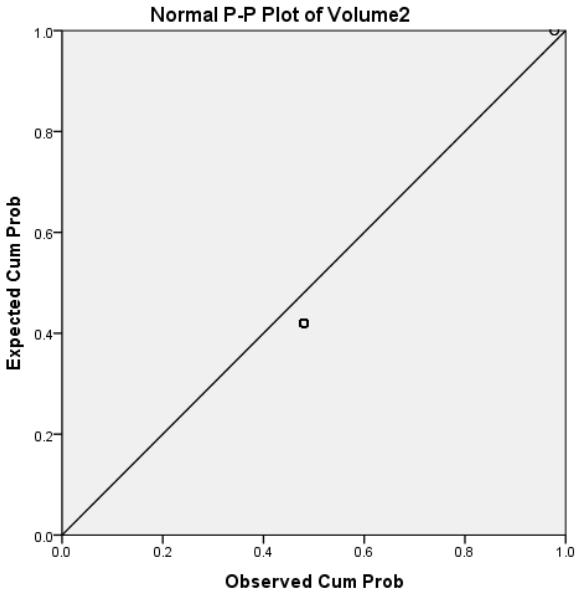
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Nominal by Nominal	Phi	.312			.302
	Cramer's V	.312			.302
Interval by Interval	Pearson's R	.233	.080	1.658	.104[c]
Ordinal by Ordinal	Spearman Correlation	.255	.088	1.824	.074[c]
N of Valid Cases		50			

Mean : 1.04

P. value : 0.002



Patients platelets volume



Control

Table (3-22) Crosstabulation between platelets distribution width of patients and control

Chi-Square Tests

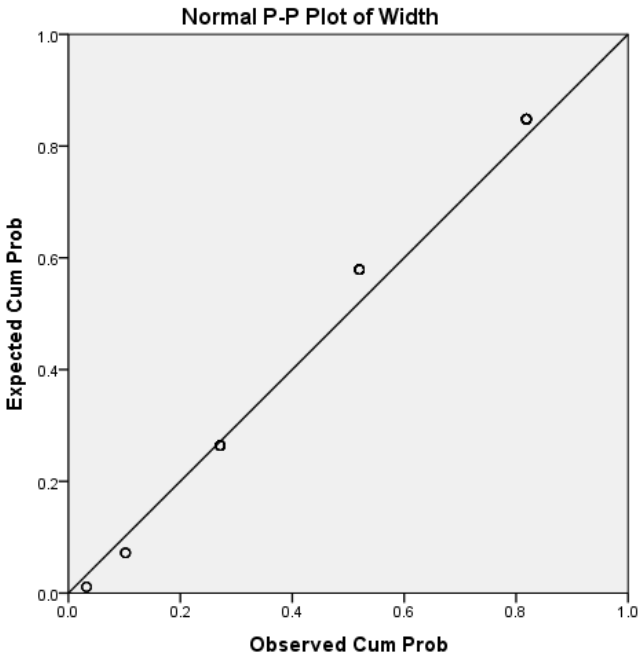
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3.225[a]	8	.919
Likelihood Ratio	4.451	8	.814
Linear-by-Linear Association	1.956	1	.162
N of Valid Cases	50		

Symmetric Measures

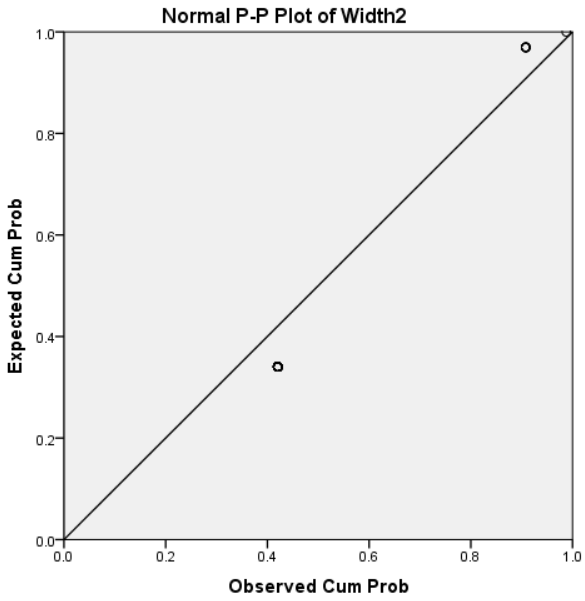
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Nominal by Nominal	Phi	.254			.919
	Cramer's V	.180			.919
Interval by Interval	Pearson's R	.200	.098	1.413	.164[c]
Ordinal by Ordinal	Spearman Correlation	.176	.122	1.237	.222[c]
N of Valid Cases		50			

Mean : 1.18

P. value : 0.006



Patients distribution width



Control

4. Discussion, Conclusion, Recommendation

4-1 Discussion:

The MPV and platelet count are indicator of thrombotic potential, and risk factors for microvascular complications in diabetics .MPV is an indicator of the average size and activity of platelets, with a higher MPV value indicating a large average platelet size. larger platelets synthesize more thromboxane A2,are able to aggregate better ,and are able to secret more serotonin and beta thromboglobulin than smaller platelets, our study revealed a higher significant levels of MPV and PDW in diabetic patients compared to control ,this results show a complete agreement with other studies .

Astudy done in brasil 2013 -2014 , results that platelet indices MPV and PDW were found to be raised in patients with T2 DM compare to non-diabetics, which agree with our study (34).

A study done in Sudan infidal specialized hospital Khartoum state 2015, this study revealed higher MPV and PDW in diabetic than control group which agree with our study (39).

Another study done by papanas et al 2004, they found that MPV was significantly higher in diabetics than non-diabetics which agreement with our study (36).

Other study in Sudan in suba university hospital 2011,the results of this study all platelet indices were significantly raised in diabetic patients compared with non-diabeticindividuals. And this also agree with our study(38).

4-2 Conclusion:

Plt indices are significantly affected by type 2 DM. Their clinical utility and association with a disease activity in patients with DM should be further investigated.

This study concluded a higher mean platelet volume and platelet distribution width in diabetic patients than controls.

4-3 Recommendations:

1-Increase the number of samples to obtain confidence results .

2- Further studies were needed to give accurate results .like HB A1c .

3- Platelet indices might be used simple and cost –effective laboratory test in the follow up of diabetes mellitus along with HbA1C and therapy help to reduce the morbidity and mortality.

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Appendix

Questionnaire

University of ElsheikhAbdallahElbadri
Collage of Health Science
Medical Laboratory Science

Questionnaire of research (Assessment of platelet indices in patients with type 2 Diabetes Mellitus in Atbara City).

- ID……..
- Date…….
- Gender : Male Female
- Age……
- Height…….m.
- Weight……kg.
- Body mass…….kg/m2
- Duration of disease…….
- Family history of disease: Yes No
- Type of treatment : Insulin Drugs
  No treatment
- Complication
  ……
  ……
  ……
  ……
- Wounds : Found Not found
  Wounds healing: Fast
  Slow
- Other disease
  ……
  ……
  ……
  ……

2ml of blood taken in EDTA vasocontainer:-

- Platelets Count……
- Platelets Parameters :-
  Main Platelets volume……fl.
  Platelets distribution width……..fl.
- Sugar level : Fasting blood glucose
  After 2hours

INFORMED CONSENT FOR COLLECTION OF BLOOD SAMPLES FOR REASEARCH

This sample is being collected solely for purpose of research .The research to assess platelets indices in type2 diabetic patient in Atbara town . The procedure for sample collection involves only the withdrawal of 2-3 ml of blood. It is such a harmless process .The results of the study may not be of immediate benefit to the patient. Complete confidentiality will be maintained in the handling and processing of samples.

The above statement has been read out or explained to me, and having understood the same, I put my signature or thumb impression. I hereby consent to collection of the blood sample of myself.

Patient name: Phone number:

Address: signature/ left thumb impression of patient:

Date:

استمارة موافقه للأشخاص المشاركين في الدراسة

هذه الدراسة لغرض البحث العلمي فقط وهى بغرض حساب متوسط حجم الصفائح الدموية و متوسط عرض توزيع الصفائح الدموية عند مرضى السكري وتتطلب أخذ ٢-٣ مل من الدم ولا يوجد اذى او خطورة تنتج منها عليك و حال موافقتك على المشاركة في هذه الدراسة سيبقى اسمك قيد الكتمان كما يكون لن يكون هنالك أي تعويض مالي. لقد اطلعت على استمارة الموافقة وادركت مضمونها واطلعني الباحث عن فوائد بحثه واهميته العلمية والعملية وبناء عليه فإني حراً مختاراً وبمحض إرادتي اوافق على المشاركة في هذه الدراسة كما اوضح بان مشاركتي فيها طوعا منى , وأن باستطاعتي رفض المشاركة كما أن بإمكاني أن لا اجيب على أي سؤال لا ارغب في اجابته , كما تم إعلامي بان مشاركتي بالبحث لن تحملني أي نفقات او مسائله من شانها الضرر بمهنتي او شخصي . وان المعلومات الناتجة عن مشاركتي سوف تعامل بسريه تامه ولن يطلع عليها أي شخص غير معنى بالبحث وان هذه المعلومات ونتائجها هي لأغراض علميه فقط ولن تكون هنالك اشاره الى شخص او عائلتي في أي منشور عن هذه الدراسة ولأجل هذا فإني اوافق بمشاركتي في هذه الدراسة.

اسم المشارك: رقم التلفون:

التوقيع: العنوان:

التاريخ :