Pro Index | Journal of Science in Medicine and Life
Volume: 4 Issue: 1 Year: 2026
ISSN: 2992-9202 | http://journals.proindex.uz

# Significance of Platelet Indices Other Than Thrombocytopenia as Severity Marker in Preeclamptic Cases Attending Al-Elwiyah Maternity Teaching Hospital

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***Abstract:*** **Background:** Preeclampsia is a serious pregnancy complication, affecting 2-8% of pregnancies worldwide, characterized by elevated blood pressure, and proteinuria. It poses significant maternal and fetal health risks, necessitating better diagnostics and prognostics tools. Platelets play a complex role in preeclampsia, and their indices may offer insights into the condition's severity and progression, aiding in early detection and treatment guidance.

**Aim of the study:** This study evaluates platelet indices (MPV, PDW, PCT) in non-thrombocytopenic preeclampsia cases at Al-Elwiyah Maternity Teaching Hospital to gauge preeclampsia severity.

**Patients and methods:** This cross-sectional study was conducted at Al-Elwiya Maternity Teaching Hospital from January 2023 to December 2023, involving 300 women (150 with preeclampsia, 150 healthy pregnant as controls). detailed data collected through questionnaires, physical examinations, and laboratory analyses of platelet indices (MPV, PLT, PCT, PDW). The cases were compared according to the rate of complications and predictive ability of platelet indices.

**Results:** The maternal age, gestational age, and parity did not significantly differ between groups. Liver enzymes were markedly elevated in severe cases. Platelet count and PCT were lower in severe preeclampsia, while platelet indices (MPV, PDW) were higher. ROC analysis demonstrated excellent discriminative ability for MPV (AUC=0.95), PDW (AUC=0.926), and PCT (AUC=0.945) in predicting severe preeclampsia, with (MPV: Sensitivity 81.3%, Specificity 85.8%; PDW: Sensitivity 92%, Specificity 86.7%; PCT: Sensitivity 70.7%, Specificity 94.7%).

**Conclusion:** Platelet indices, particularly MPV and PDW, correlate strongly with preeclampsia severity. MPV and PDW are valuable for severe cases, while PCT is more specific but less sensitive. These indices can aid in early preeclampsia severity assessment and management.

***Key points:*** Preeclampsia, platelet distribution width, mean platelet volume, platecrit.

## 1. INTRODUCTION

### 1.1. Background

Preeclampsia stands as a massive complication in pregnancy, characterized by its potential for severe consequences. This hypertensive disorder, traditionally marked by elevated blood pressure and the presence of protein in the urine, remains one of leading causes of maternal and fetal morbidity and mortality worldwide. Despite advances in obstetric medicine, preeclampsia affects approximately 2-8% of pregnancies globally, manifesting a spectrum of severity that can range

from mild to life-threatening conditions for both the mother and the unborn child. The complexity and unpredictability of preeclampsia ( PE) not only pose significant challenges in prenatal care but also necessitate a deeper understanding of its diagnosis and prognosis. As such, the exploration of preeclampsia's implications, particularly through the lens of platelet indices, is not only pertinent but vital in the quest to enhance maternal and fetal health outcomes[1].

### 1.2. Definition of PE

Pre-eclampsia is defined as new hypertension presenting after 20 weeks with one or more new-onset features, including significant proteinuria or maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological complications or hematological complications. Severe pre-eclampsia is defined as having a blood pressure of ≥160 mmHg systolic or 110 mmHg diastolic, with worsening maternal organ dysfunction (such as hemolysis, elevated liver function tests and low platelets, also known as HELLP syndrome) or worsening fetal growth restriction. Early onset-preeclampsia refers to an onset of the disorder before 34 weeks, whereas late-onset preeclampsia develops at or after 34 weeks of gestation[2].

### 1.3. Epidemiology of PE

Preeclampsia considered as one of the leading causes of maternal and perinatal morbidity and mortality globally. Approximately, one-tenth of all maternal mortality in Africa and Asia and one-quarter in Latin America are associated with hypertensive diseases in pregnancy, a category that encompasses PE. Pre-eclampsia affects about 2–8% of all pregnancies worldwide [3]. In the UK, despite improvements over recent years, PE remains a significant cause of direct maternal death, with six cases reported in the latest triennial report. Up to 5% of women will develop PE in their first pregnancy and although the overwhelming majority of these will have successful pregnancy outcomes, the condition can lead to severe multisystem complications as cerebral hemorrhage, hepatic and renal dysfunction and respiratory compromise [4, 5]. While in Iraq the prevalence of preeclampsia among pregnant women is reported to be 4.79% and hypertensive disorder is the third cause of maternal death in Iraq in the last few years [6].

### 1.4. Clinical presentations

The clinical presentation of PE may be insidious or fulminant. Signs and symptoms of PE can include: [7-9].

- ✓ High blood pressure; 140/90 or higher.
- ✓ Swelling (edema) with weight gains of more than 4 pounds in a week.
- ✓ Decreased urine output.
- ✓ Blurred vision, usually in the form of flashing lights or inability to tolerate bright light.
- ✓ Epigastric pain associated with impaired liver function and/or severe headaches.
- ✓ Nausea or vomiting, especially if nausea and vomiting come back after mid-pregnancy
- ✓ Abdominal pain, especially in the upper right part of the abdomen or in stomach.

Preeclampsia-eclampsia may develop before, during, or after delivery. Up to 40 % of eclamptic seizures occur before delivery; about 16 % occur > 48 hours after delivery.

### 1.5. Diagnostic criteria

Pre-eclampsia is diagnosed when a pregnant woman develops [10]:

- ➢ Blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic on two separate readings taken at least four to six hours apart after 20 weeks' gestation in an individual with previously normal blood pressure.

- In a woman with essential hypertension beginning before 20 weeks' gestational age, the diagnostic criteria are: an increase in systolic BP of ≥30 mmHg or an increase in diastolic BP of ≥15 mmHg.
- Proteinuria ≥ 0.3 grams (300 mg) or more of protein in a 24-hour urine sample or urinary protein to creatinine ratio ≥0.3 or a urine dipstick reading of 1+ or greater (dipstick reading should be used if other quantitative methods are not available) [11].

In the absence of proteinuria, the presence of new-onset hypertension and the new onset of one or more of the following is suggestive of PE [12]:

- ✓ Evidence of kidney dysfunction (oliguria, elevated creatinine levels)
- ✓ Impaired liver function.
- ✓ Thrombocytopenia (platelet count <100,000/microliter).
- ✓ Pulmonary edema.
- ✓ Ankle edema (pitting type).
- ✓ Cerebral or visual disturbances.

### 1.6. Risk Factor

**Table 1-1: Risk factors of preeclampsia[2].**

| Risk Factors | |
|---|---|
| **Major** | **Minor** |
| Prior preeclampsia | Multiple gestations |
| Renal disease | Obesity (BMI ≥ 30 kg/m²) |
| Chronic hypertension | Family history of preeclampsia |
| Diabetes mellitus | Advanced maternal age (≥ 35 years) |
| Primiparity | Excessive gestational weight gain (≥ 16 kg) |
| Antiphospholipid antibody syndrome | Strong family history of cardiovascular disease |
| Systemic lupus erythematosus | |

### 1.7. Pathogenesis

The pathogenesis of preeclampsia, though not fully elucidated, is generally believed to be initiated by placental ischemia followed by placental release of antiangiogenic factors into the circulation[13]. The blueprint for establishing PE is determined at the outset of pregnancy when placental trophoblast invades the maternal uterine spiral arteries at the time of implantation. In pregnancies destined to be complicated by PE, transformation of the spiral arteries is impaired, with suboptimal remodeling of small-capacitance constricted vessels into dilated large-capacitance conduits [14]. This remodeling is meant to increase the supply of oxygen and nutrients to the fetus. In doing so, the cytotrophoblasts upregulate expression of molecules that are important to uterine invasion such as those from the vascular endothelial growth factor (VEGF) family (e.g., VEGF-A, VEGF-C, placental growth factor [PlGF]). In preeclampsia, however, this process is incomplete, thus resulting in placental ischemia and the triggering of hypoxia inducible factors and other placenta-derived factors[13]. Similarly, expression of the important VEGF family of molecules is downregulated, yet its inhibitor is upregulated. Several groups have demonstrated that the soluble fms-like tyrosine kinase1 (sFlt-1) is upregulated in placentae of preeclamptic women. sFlt-1 is a circulating decoy receptor that binds to PlGF, preventing their interaction with cell surface receptors on endothelial cells and leading to endothelial dysfunction[15].Early studies showed that sFlt1 levels were elevated in the sera of preeclamptic women throughout their pregnancies and that their upregulation was associated with decreased levels of circulating free VEGF and free PlGF. VEGF induces nitric oxide formation that neutralizes reactive oxygen species and vasoconstrictor signaling. In the presence of excess sFlt-1, lack of endothelial nitric oxide leads to vasoconstrictor sensitivity and hypertension[16]. Similarly, a second placenta-derived protein, soluble endoglin (sEng), was later

found to be upregulated in preeclampsia. sEng is an inhibitory factor that binds to transforming growth factor beta (TGF-β) in circulation, disallowing its binding to the in situ TGF-β receptor. Inactivation of both VEGF and/or TGF-β signaling have led to impaired endothelium-mediated vasodilation and vascular autoregulation. [17].

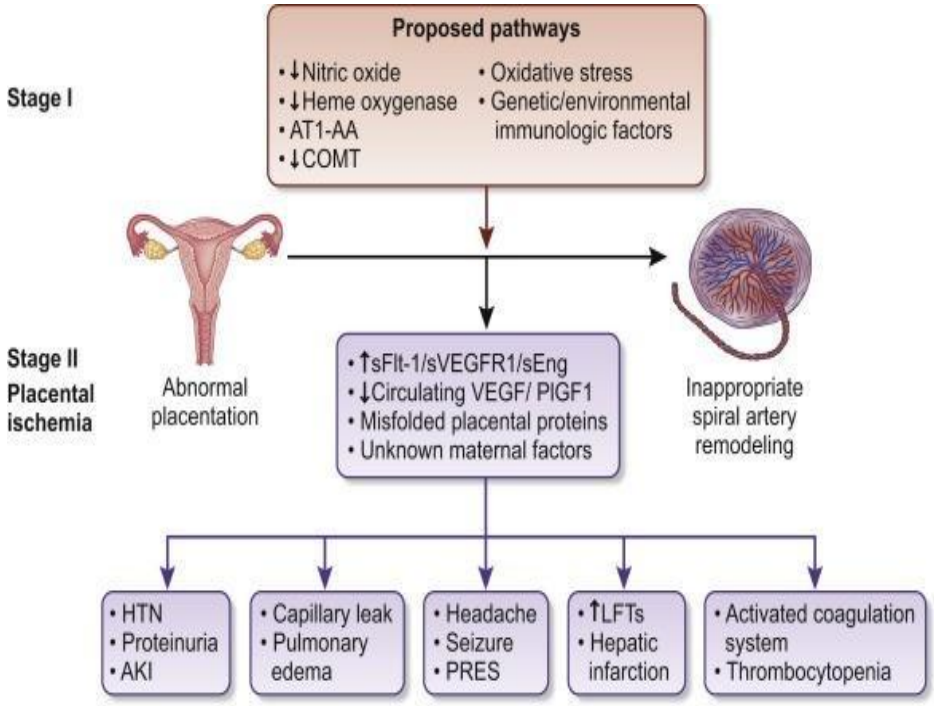


**Figure 1-1: Pathogenesis for preeclampsia: two-stage model[18].**

AKI, acute kidney injury; AT1-AA, autoantibodies to angiotensin receptor 1; COMT, catechol-O-methyltransferase; HTN, hypertension; LFT, liver function test; PlGF1, placental growth factor 1; PRES, posterior reversible encephalopathy syndrome; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase 1; sVEGFR1, soluble vascular endothelial growth factor receptor 1; VEGF, vascular endothelial growth factor.

### 1.8. Classification of preeclampsia according to the Severity:

The severity of preeclampsia is a critical aspect in its classification and management, as it directly influences the treatment approach and the prognosis for both the mother and the fetus. The severity of preeclampsia is generally categorized into mild and severe forms, each with distinct clinical features, implications, and management strategies[2].

**Preeclampsia[2]:**

- **Blood Pressure:** In mild preeclampsia, blood pressure is elevated but typically not excessively high. The thresholds are usually systolic blood pressure of 140-159 mmHg and/or diastolic blood pressure of 90-109 mmHg.
- **Proteinuria:** Mild proteinuria is often present but less than what is seen in severe cases. This is typically defined as 1+ to 2+ on a dipstick urine test or a 24-hour urine protein of 300-500 mg.
- **Symptoms:** Women with mild preeclampsia may have no symptoms, or they may experience mild symptoms such as headache, swelling (edema), and weight gain.

**Severe Preeclampsia[2]:**

- **Blood Pressure:** In severe preeclampsia, blood pressure readings are typically higher, with systolic blood pressure equal to or greater than 160 mmHg and/or diastolic blood pressure equal to or greater than 110 mmHg.
- **Proteinuria:** More significant proteinuria is present, often greater than 2+ on a dipstick or more than 500 mg in a 24-hour urine collection.

- **Organ Dysfunction:** Severe preeclampsia can involve signs of organ dysfunction, such as elevated liver enzymes, renal insufficiency (evidenced by elevated creatinine), and low platelets (thrombocytopenia).
- **Neurological Features**: Severe headaches, visual disturbances (such as blurred vision or seeing spots), and hyperreflexia is more common in severe cases.
- **Pulmonary Edema and Heart Failure:** These are serious complications that can occur in severe preeclampsia.
- **HELLP Syndrome:** Some women develop this severe form of preeclampsia, characterized by hemolysis, elevated liver enzymes, and low platelet count.
- **Eclampsia**: The development of seizures in a woman with preeclampsia signifies eclampsia, a severe neurological complication[19].

### 1.9. Adverse outcomes related to pre-eclampsia

Preeclampsia can result in significant health impairment in patients during pregnancy, immediately postpartum, and beyond.

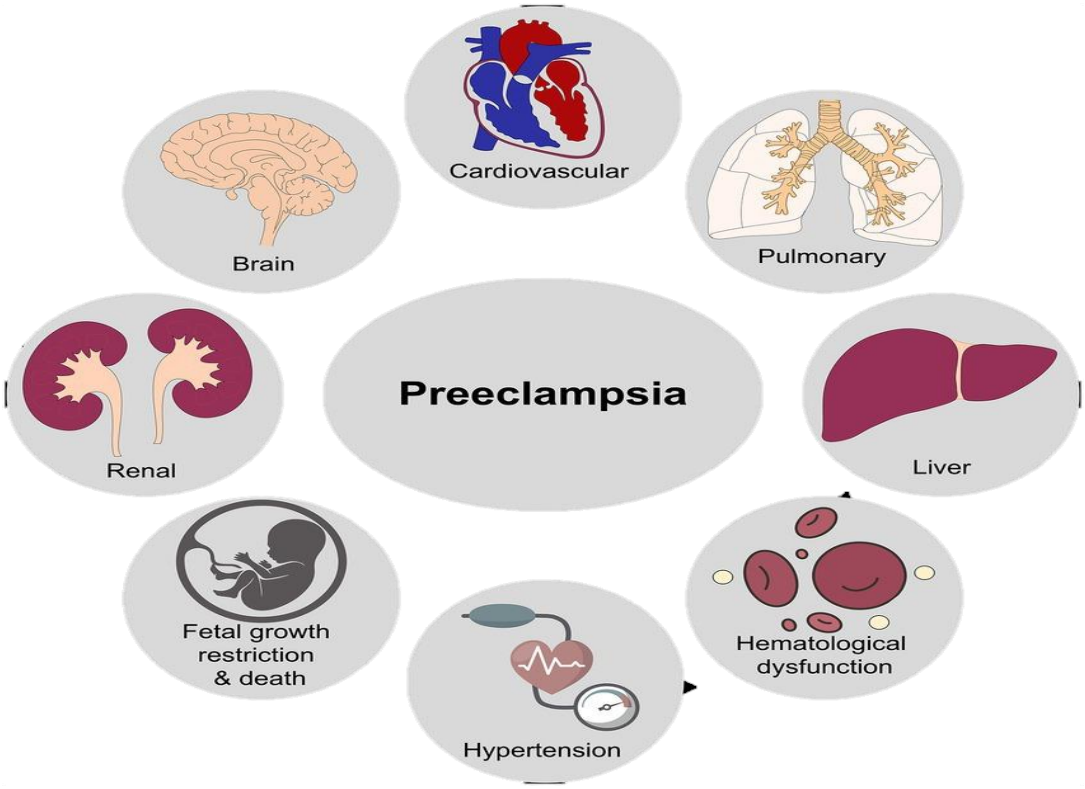


**Figure 1-2: Organ systems impacted by preeclampsia[20].**

The figure shows various organ systems affected by preeclampsia leading to short-term and long-term maternal/fetal morbidity and mortality.

#### 1.9.1. Maternal adverse outcomes

The development of preeclampsia profoundly impacts the cardiovascular system. In the short term, severe cases of preeclampsia can lead to cardiac dysfunction and severe hypertension and are also associated with peripartum cardiomyopathy[21]. Patients with preeclampsia have a two-fold increase in the subsequent development of both fatal and non-fatal ischemic heart disease. These patients demonstrate accelerated cardiovascular aging, illustrating increased overall arterial stiffness like older, postmenopausal patients[22].

The risk of the development of heart failure over the first 5 years postpartum is elevated in patients with preeclampsia, especially those with pre-existing chronic hypertension[23]. The development of preeclampsia also significantly increases the risk of sustained hypertension in the postpartum period

as well as over the course of a patient's life, developing disease earlier in life than those without a preeclampsia history[24].

Beyond the cardiovascular system, preeclampsia significantly impacts the kidneys and is the most common glomerular-based kidney disease in the world. In normal pregnancy, there is an increase in the glomerular filtration rate (GFR), resulting in a decrease in the serum creatinine value. Thus, normal creatinine values for a non-pregnant person may be pathologic in the state of pregnancy. Because of the altered physiology in pregnancy, a 30 to 40% reduction in GFR occurs prior to a significant elevation of the serum creatinine. Histologically, changes have been observed in the kidneys of people with preeclampsia, including endothelial swelling with a decrease in surface area for filtration as a result of increased subendothelial fibrinoid deposits. These changes contribute to an increased incidence of acute renal failure in pregnancy. These changes and renal pathologies can persist postpartum and are associated with significant maternal morbidity[25].

Blood cell dyscrasias and hepatic dysfunction are often observed in preeclampsia. Thrombocytopenia is observed in 30–50% of people with preeclampsia, with platelets less than $100 \times 109/L$ being diagnostic for preeclampsia with severe features. A combination of altered platelet clearance and hemolysis is thought to contribute to the thrombocytopenia seen in preeclampsia[26]. Thrombocytopenia may also be caused from the activation and consumption of platelets caused by the endothelial injury seen in preeclampsia. Hemolysis associated with preeclampsia is associated with an increased risk of poor outcomes, including acute kidney injury, blood transfusion, ICU admission, pulmonary edema, and poor neonatal outcomes. While the short-term implications on the hematologic system in patients with preeclampsia are relatively well understood, the long-term impact warrants further study[27].

Hepatic dysfunction in preeclampsia is marked by microvesicular fat changes and periportal and sinusoidal fibrin deposition in the liver parenchyma. These changes are typically transient and do not result in severe disability. Rarely, a subcapsular hematoma may form. This is potentially catastrophic, with resultant mortality rates ranging from 17 to 59% with an expanding hematoma or hepatic rupture. Rarely, patients may require a liver transplant after severe liver involvement in preeclampsia, though this is an exceedingly rare complication[28].

The nervous system is also significantly affected in pregnancy and preeclampsia. Eclamptic seizures are the most well-known neurologic sequela of preeclampsia, with an incidence of 0.5–1.5% of deliveries in developing countries but as low as 0.01–0.1% of deliveries in developed countries[29]. Patients with eclampsia have an increased risk of disseminated intravascular coagulation, acute renal failure, pulmonary edema, heart failure, cerebrovascular disease, and death. Aside from eclampsia, there is an increased risk of a cerebrovascular accident caused by uncontrolled hypertension from preeclampsia. Once patients are outside of the acute postpartum setting, their long-term risk of stroke remains elevated, with a two-fold increase in cerebrovascular accidents.

Some studies have suggested that patients with preeclampsia demonstrate long-term cognitive decline compared to those with pregnancies not impacted by preeclampsia[30].

### 1.9.2. Fetal adverse outcomes

Though preeclampsia has significant sequelae in the pregnant person, there are also important implications for the fetus. As many as 1/3 of fetuses of patients with preeclampsia will develop fetal growth restriction[31]. Fetal growth restriction itself carries an increased risk of stillbirth and neonatal death, necessitating increased healthcare visits and resultant costs as well as often inpatient admission[32]. There is a seven-fold increase in the risk of intrauterine fetal death in preeclampsia with severe features as compared to pregnancies unaffected by hypertensive disorders. With these known risks, patients with preeclampsia are extensively monitored during their pregnancy. Increased surveillance is more burdensome for the patient and costly for the healthcare system overall. If there is a high suspicion of worsening disease or a need for more monitoring, patients may be admitted for prolonged periods of time. Lastly, increased monitoring and the need for

diagnostic evaluation can result in iatrogenic preterm delivery and the associated morbidities and costs that accompany preterm birth[33].

Newborns of pregnancies affected by preeclampsia are at higher risk of being small for gestational age and of having low seven-minute APGAR scores. Children born after pregnancies affected by preeclampsia are noted to have higher systolic blood pressures and body mass indices[34]. In addition, a few small studies have demonstrated changes in brain structural and vascular anatomy along with evidence of cognitive changes[35].

### 1.10. Platelet indices in normal pregnancy

Platelet indices, including Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), and Plateletcrit (PCT), undergo various changes during pregnancy that warrant attention and understanding.

**Mean Platelet Volume (MPV):** During pregnancy, platelets play a crucial role in maintaining hemostasis. The mean platelet volume (MPV), which reflects the average size of platelets in the blood, undergoes interesting changes. As an expectant mother progresses through her pregnancy, MPV tends to decrease. This reduction is thought to be an adaptive response to prevent excessive bleeding during childbirth and the immediate postpartum period[36].

One theory suggests that smaller platelets are more efficient at forming stable clots. By reducing the average platelet size, the body ensures effective clot formation without compromising the overall platelet count. Additionally, the decreased MPV may be related to hormonal changes during pregnancy, including elevated estrogen levels[36].

**Platelet Distribution Width (PDW):**

The platelet distribution width (PDW) measures the variation in platelet size. While PDW may exhibit minor fluctuations during healthy pregnancies, it generally remains within acceptable limits. PDW is an indirect indicator of platelet heterogeneity. PDW reflects platelet production and turnover. Changes in PDW can signal underlying platelet disorders or altered megakaryocyte function. In the context of pregnancy, PDW variations may be influenced by factors such as nutritional status, inflammation, and hormonal shifts[37].

**Plateletcrit (PCT):**

The plateletcrit represents the proportion of platelets in the total blood volume. It is calculated as the product of platelet count and mean platelet volume. During pregnancy, PCT may decrease slightly due to increased platelet consumption[38].

These indices offer valuable information for assessing a pregnant woman's hemostatic status and ensuring appropriate care throughout pregnancy and childbirth. Monitoring these parameters and recognizing significant deviations can aid in early detection and management of potential complications[39].

### 1.11. Platelets and Their General Role in Preeclampsia

Platelets are small, disc-shaped cells, primarily known for their crucial role in blood clotting and wound healing. However, these tiny cells play a more complex and multifaceted role in the body, including their involvement in various physiological processes and pathologies. When it comes to preeclampsia, platelets have garnered significant attention for their potential role in both the development and complications of this condition[40].

**Normal Platelet Function:**

To understand the role of platelets in preeclampsia, it's essential to first grasp their normal function. Platelets are produced in the bone marrow and circulate in the blood in an inactive state. When blood vessels are injured or damaged, a series of events are triggered to form a blood clot, preventing excessive bleeding. Platelets play a central role in this process by adhering to the site of injury, aggregating together, and releasing chemical signals that promote clot formation[41].

**Platelets in Preeclampsia:**

Preeclampsia is known to affect multiple organ systems, including the vascular endothelium, liver, kidney, and the hematological system. Thrombocytopenia is one of the hematological manifestations often observed in women with preeclampsia. Thrombocytopenia is a condition characterized by a reduced number of platelets in the blood, resulting in an abnormally low platelet count. A normal platelet count ranges from 150,000 to 450,000 platelets per microliter of blood. Thrombocytopenia is typically diagnosed when the platelet count falls below this normal range. This phenomenon can be attributed to various factors associated with the pathophysiology of preeclampsia.

In preeclampsia, the relationship between platelets and the vascular system becomes perturbed.

Platelets are integral to this vascular dysfunction in several ways:

1. Platelet Activation: Preeclampsia often involves increased activation of platelets. Activated platelets are more likely to aggregate and form clots within blood vessels. This heightened platelet activation can contribute to the development of hypertension and endothelial dysfunction seen in preeclampsia[(42)].
2. Endothelial Damage: Platelets can adhere to and damage the inner lining of blood vessels, known as the endothelium. In preeclampsia, this endothelial damage is a key feature, and platelets may contribute to this process by initiating inflammatory responses and oxidative stress[(43)].
3. Placental Dysfunction: Preeclampsia is thought to originate in the placenta, where abnormal development and function can lead to an imbalance in substances released into the maternal circulation. Platelets may become activated in response to placental factors, further exacerbating the vascular issues associated with preeclampsia[(42)].
4. Role in Inflammation: Platelets are not only involved in clot formation but also in the body's inflammatory response. In preeclampsia, there is often an underlying inflammatory state, and platelets can release pro-inflammatory molecules that contribute to this inflammation[(44)].
5. Interaction with Immune Cells: Platelets can interact with immune cells in the bloodstream, potentially exacerbating the immune response that contributes to preeclampsia[(43)].

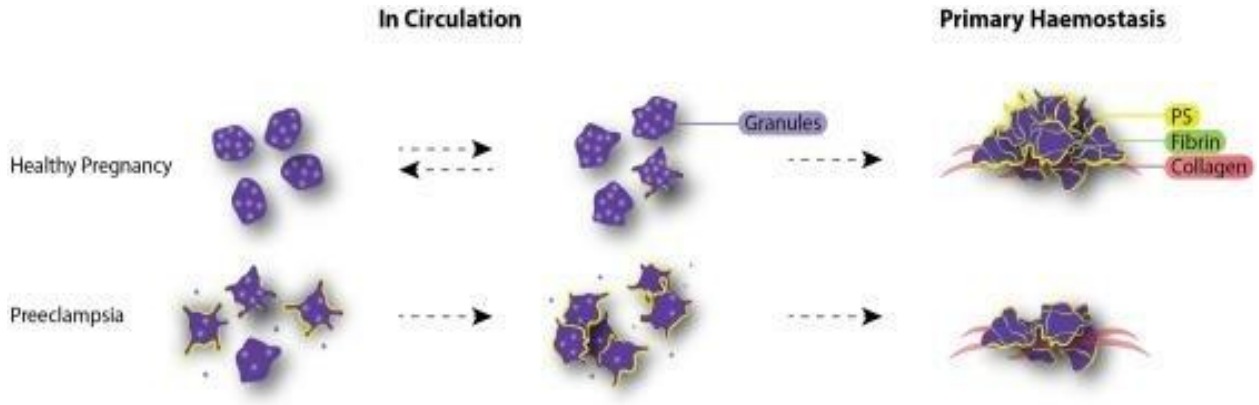


**Figure 1-3: Platelet phenotypic duality in preeclampsia[(45)].**

Platelets in healthy pregnancy show signs of mild activation and priming, consistent with a prothrombotic state.In Preeclampsia platelets, however, are preactivated in circulation, proaggregatory, partially degranulated, and may circulate as microaggregates/microthrombi.

**Clinical Significance of Thrombocytopenia in Preeclampsia:**

1. Severity Indicator: Thrombocytopenia in preeclampsia is considered a marker of disease severity. It often accompanies severe forms of preeclampsia and can be indicative of organ dysfunction,

particularly in the liver and kidneys. Monitoring platelet counts in preeclamptic women is essential for assessing the severity of the condition and guiding clinical management.

2. Risk of Bleeding: A low platelet count increases the risk of bleeding, both during pregnancy and childbirth. This risk is a concern for both the mother and the fetus, as excessive bleeding can lead to complications such as postpartum hemorrhage.

3. Predictive Value: Thrombocytopenia can serve as a predictive marker for the development of preeclampsia. Some studies have suggested that a low platelet count earlier in pregnancy may be associated with an increased risk of developing preeclampsia later in gestation.

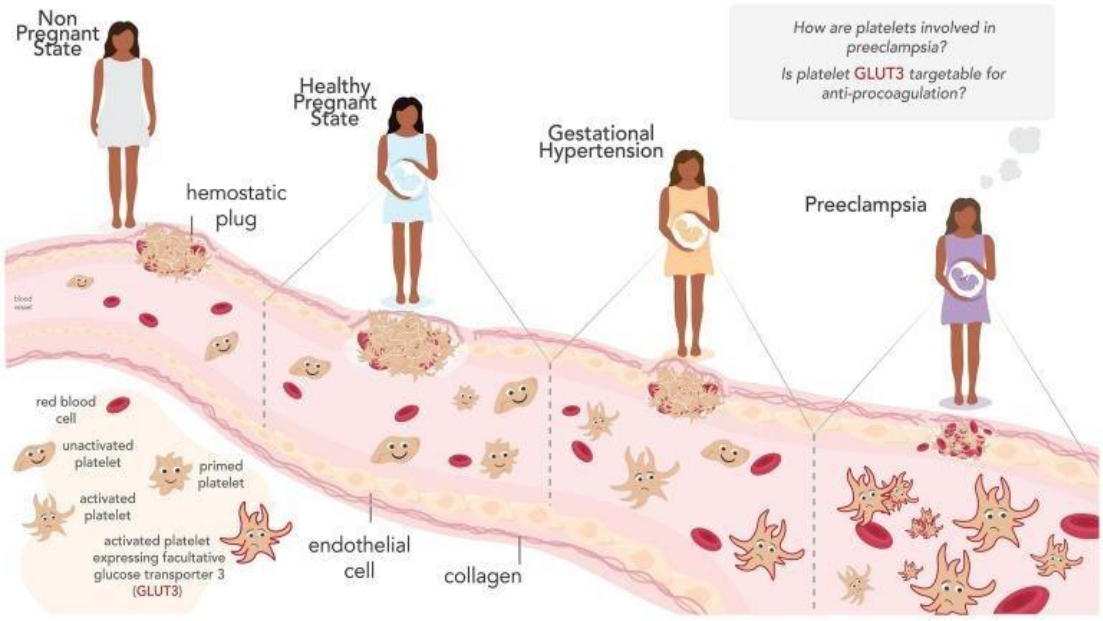


**Figure 1-4: Platelet activation in preeclampsia[45].**

Preeclampsia platelets are preactivated, proaggregatory, and prothrombotic in circulation.

**Platelet indices**

Complete blood count (CBC) tests with automated hematology analyzers are one of the most commonly ordered tests in clinical laboratories. Modern hematology analyzers in routine diagnostic use, which measure platelet indices (PIs), use impedance counting or optical light scatter counting techniques.

Platelet indices are biomarkers of platelet activation. They allow extensive clinical investigations focusing on the diagnostic and prognostic values in a variety of settings without bringing extra costs. Among these platelet indices, plateletcrit (PCT), mean platelet volume (MPV), and platelet distribution width (PDW) are a group of platelet parameters determined together in automatic CBC profiles; they are related to platelets' morphology and proliferation kinetics[46].

**A. Mean platelet volume (MPV):**

The mean platelet volume (MPV) is a precise measurement of their dimension, calculated by hematological analyzers on the basis of volume distribution during routine blood morphology test. MPV ranges between 9 and 13.0 femtoliter (fl), whereas the percentage of large platelets should amount to 0.2-5.0% of the whole platelet population [47].

In physiological conditions, MPV is inversely proportional to the platelet count, which is associated with hemostasis maintenance and preservation of constant platelet mass. This means that the increased production of platelets is accompanied by a reduction in their mean volume. In various pathologies, this physiological proportion is disturbed. Markedly enhanced or abnormal thrombocytopoiesis, increased wear, or the effect of activating factors on blood platelets may lead to changes in the proportions between MPV and PLT [48].

Therefore, possible application of these parameters to the diagnosis of certain diseases has been suggested. Moreover, MPV correlates with platelet activity and is thus considered a marker of platelet activity[48].

Blood platelets are not a homogenous population. Those with increased MPV (>15 fl) are often younger and characterized by higher reactivity than those with normal MPV. Their generation is associated with marked activation of megakaryocytes by cytokines, which increases the ploidy of these cells and enhances the release of larger platelets [49].

It is also suggested that large thrombocytes show a greater content of cell granules, display higher expression of adhesion molecules, and undergo faster activation, which results in platelet hyperactivity and increased risk of clot formation. Elevated MPV correlates with increased platelet aggregation, enhanced synthesis, and release of thromboxane TXA2 and β-thromboglobulin[50] .

In healthy individuals, the increased platelet count, via feedback, leads to considerable inhibition of Thrombopoietin synthesis by the liver and in consequence causes platelet release by megakaryocytes, which is to maintain constant platelet mass. However, in patients with ongoing inflammation, the increasing concentration of proinflammatory cytokines, mainly IL-6, can lead to platelet release. This is associated with the stimulation of thrombopoietin generation by IL-6 and with a direct effect of this cytokine on megakaryocytes. IL-6 causes an increase in the ploidy of megakaryocytic nuclei and an increase in cytoplasm volume, which in consequence leads to the production of a large number of blood platelets[50].

The course of an inflammatory condition is also associated with increased percentage of large platelets, probably due to intracellular synthesis of procoagulatory and proinflammatory factors, degranulation of granules, and initiation of the platelet pool stored in the spleen. Simultaneously, these cells rapidly migrate to the site of inflammation where they undergo activation and wear. This seems to explain the drop in MPV in patients with ongoing inflammation[48].

Many studies investigated the role of increased MPV and found that it is associated with a higher risk of acute cardiac incidents[51], with a risk of acute stroke [148], in tuberculosis it is associated with intensity of inflammation [149], being a marker of Crohn's disease activity[52], associated with retinopathy and nephropathy[53], being potential marker of liver cancer in patients with chronic liver diseases and many other diseases[54].

**B. Platelet distribution width (PDW):**

Platelet distribution width (PDW) is a regular parameter in blood routine examination which reflects variation of platelet size distribution with a range from 9-17%. There is always a morphological change when platelet is activated in the environment of inflammation. Thus, PDW can be utilized as a sign of activated platelet releasing in some inflammatory diseases. Studies have demonstrated that PDW level changes under specific conditions compared to healthy individuals[55].

Increased PDW values have been reported in patients with diabetes mellitus[56], cancer[57], cardio-cerebrovascular, respiratory disorders[58], and chronic obstructive pulmonary disease [59]. Moreover, higher PDW levels have recently been reported to be associated with increased morbidity and mortality among patients with critical illness [60].

**C. Plateletcrit (PCT):**

PCT is the volume occupied by platelets in the blood as a percentage and calculated according to the formula PCT = platelet count × MPV / 10,000[61]. Under physiological conditions, the amount of platelets in the blood is maintained in an equilibrium state by regeneration and elimination. The normal range for PCT is 0.22–0.24%. In healthy subjects, platelet mass is closely regulated to keep it constant, while MPV is inversely related to platelet counts. Genetic and acquired factors, such as race, age, smoking status, alcohol consumption, and physical activity, modify blood platelet count and MPV[62].

### 1.12. Platelets indices changes in preeclampsia

The assessment of platelet indices, including mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT), can offer valuable insights into the severity of preeclampsia. These indices, derived from routine blood tests, provide additional information about platelet characteristics that can be indicative of the condition's progression and severity[27].

**1. Mean Platelet Volume (MPV):**

- Platelet Size Variation: MPV measures the average size of platelets in the blood. In preeclampsia, increased platelet activation and consumption can lead to the production of smaller, younger platelets. Elevated MPV may indicate platelet destruction and regeneration as the body tries to compensate for platelet loss[63].
- **Indicator of Platelet Function**: Higher MPV values have been associated with increased platelet reactivity and a greater potential to form blood clots. In severe preeclampsia, where there is a heightened risk of clot formation, elevated MPV could signify an increased thrombotic tendency[64].

**2. Platelet Distribution Width (PDW)**:

- **Platelet Size Heterogeneity:** PDW measures the variation in platelet size. In preeclampsia, platelet activation and destruction can result in a wider range of platelet sizes, leading to an elevated PDW. This heterogeneity suggests ongoing platelet turnover and abnormal platelet production[65].
- **Risk of Bleeding:** A high PDW may also indicate an increased risk of bleeding, as larger platelets are more effective in forming clots. This paradoxical situation, with both increased clotting potential and bleeding risk, is characteristic of preeclampsia's complex vascular pathology[66].

**3. Platelet Crit (PCT):**

- **Platelet Concentration**: PCT reflects the proportion of platelets in the total blood volume. In severe preeclampsia, where there may be platelet consumption and reduced production, PCT values tend to decrease. A low PCT can indicate a relative depletion of platelets in circulation[67].
- **Severity Assessment:** Monitoring PCT can help assess the severity of thrombocytopenia, a common complication of severe preeclampsia. Severe thrombocytopenia, reflected by a significantly decreased PCT, is associated with a higher risk of bleeding and organ dysfunction[68].

**Why These Indices Could be a Potential Important Marker:**

1. Early Detection: Changes in platelet indices like MPV, PDW, and PCT can be observed before the platelet count drops significantly. This means they can serve as early indicators of platelet abnormalities in preeclampsia[69].
2. Severity Stratification: These indices provide a more nuanced view of platelet function and characteristics beyond the platelet count alone. They allow healthcare providers to stratify the severity of preeclampsia more accurately[70].
3. Treatment Guidance: Understanding platelet indices can guide treatment decisions. For instance, if MPV and PDW are elevated, there may be a need for antiplatelet therapies to mitigate the risk of clot formation. Conversely, if PCT is significantly reduced, it may warrant closer monitoring and intervention to prevent bleeding complications[71].

Given the high prevalence and significant complication rates of preeclampsia in Iraq, there is a pressing need to identify more sensitive and specific markers for its early detection and severity assessment. This study aims to investigate the significance of platelet indices other than thrombocytopenia as potential severity markers in preeclamptic cases. By focusing on a cohort from

Al-Elwiyah Maternity Teaching Hospital, the study seeks to contribute to the existing literature by providing region-specific data, enhancing our understanding of preeclampsia's pathophysiology, and informing clinical practice for better patient outcomes.

### 1.13. Aim of the Study

This study evaluates platelet indices (MPV, PDW, PCT) in non-thrombocytopenic preeclampsia cases at Al-Elwiyah Maternity Teaching Hospital to gauge preeclampsia severity.

## *Chapter two*

## *Patients & methods*

## 2. PATIENTS AND METHODS

### 2.1. Study Design, Setting and Data Collection Time

This was a cross-sectional study that conducted in the Department of Obstetrics and Gynecology at Al-Elwiya Maternity Teaching Hospital during a period extended from 1st of January 2023 to 1st of December 2023

### 2.2. Study patients and sample size

The study included 300 women who presented to Al-Elwiyah Maternity Teaching Hospital and admitted to obstetrical ward, and divided into two groups:

The case group included 150 women with preeclampsia (75 cases of mild preeclampsia, and 75 cases of severe preeclampsia).

The control group included 150 healthy pregnant women with matched maternal and gestational age and BMI with the case group.

### 2.3. Inclusion criteria

- Preeclampsia Diagnosis: Patients diagnosed with preeclampsia as per established medical guidelines.
- Patient Consent: Willingness to participate in the study, with informed consent.
- Hospital Attendance: Patients attending Al-Elwiyah Maternity Teaching Hospital during the study period.
- Full Blood Count Data Available: Necessary for evaluating platelet indices (mean platelet volume, platelet distribution width, plateletcrit).

### 2.4. Exclusion criteria

- Other Pregnancy Complications: Such as gestational diabetes, chronic hypertension, or pre-existing medical conditions that could affect platelet counts (like systemic lupus erythematosus, thrombotic thrombocytopenic purpura, etc.).
- Cases of preeclampsia associated with thrombocytopenia (platelet count <150 x 103), cases with HELLP syndrome or DIC.
- Medication Use: Drugs known to affect platelet function or count (ex: Aspirin, heparin, etc.).
- Incomplete Medical Records: Lack of sufficient data to assess platelet indices.
- Multiple Pregnancies (as this could have effect on the values of these parameters and could not make it standardized for the sake of comparison).

### 2.5. Ethical considerations and official approvals

Verbal permission was obtained from each patient prior to collecting data, and information was anonymous. Names were removed and replaced by identification codes. All information kept confidential in a password secured laptop and data used exclusively for the research purposes."

**Administrative approvals were granted from the following**

1. The Council of Iraqi Board of Medical Specialization.
2. Approval and agreement of the Department of Obstetrics and Gynecology at Al-Elwiyah Maternity Teaching Hospital.

### 2.6. Data collection:

We developed a thorough questionnaire that served as the main tool for data collection in the current study.

#### 2.6.1. Maternal Data:

The questionnaire had sections for the mother's specific ID, age, and BMI as well as for her parity (the number of children she has had) and gestational age (GA) at the admission. Additionally, information on the mother's past health and obstetric history, including any problems with pregnancy or delivery, was gathered.

#### 2.6.2. Physical Examination:

After being admitted, a comprehensive physical examination was conducted, and the results were documented. This comprised measurements of overall health as well as checking of vital signs.

- **Preeclampsia Diagnosis**:
- **Blood Pressure Measurement**: Blood pressure was measured using a mercurial sphygmomanometer after the patient had rested for 15 minutes. If the BP was ≥ 140/90 mm Hg but < 160/110 mm Hg, it was reassessed after four hours. Persistently elevated BP readings at or above this threshold prompted further testing.

✓ For BP ≥ 140/90 mm Hg but < 160/110 mm Hg: A urine sample was tested for albumin if the second BP reading remained elevated. A positive result confirmed a preeclampsia diagnosis, and the patient was included in the study.

✓ For BP ≥ 160/110 mm Hg: A urine sample for albumin was requested immediately without the 4-hour waiting period. A positive result confirmed a preeclampsia diagnosis.

**Sonographic Investigations**

- **Sonographic Examination**: Patients were also subjected to a sonographic examination as part of the evaluation process.

### 2.7. Definitions

- **Mild Preeclampsia**

✓ **Blood Pressure**: Systolic blood pressure (SBP) between 140 mm Hg and 159 mm Hg, or diastolic blood pressure (DBP) between 90 mm Hg and 109 mm Hg, measured on two occasions at least 4 hours apart.

✓ **Proteinuria**: dipstick test to estimate how many protein pluses.

✓ **Symptoms**: May include mild headache, slight swelling of the hands and feet (edema), but generally lacks more severe symptoms observed in severe preeclampsia.

- **Severe Preeclampsia**

✓ **Blood Pressure**: SBP ≥ 160 mm Hg or DBP ≥ 110 mm Hg, measured on two separate occasions, at least 4 hours apart, while the patient is on bed rest.

✓ **Other Symptoms and Signs**: Includes one or more of the following – severe headaches, visual disturbances (such as blurred vision, seeing spots), intense upper abdominal pain, impaired liver function (elevated liver enzymes), pulmonary edema, or signs of renal insufficiency.

### 2.8. Laboratory analysis:

- ✓ **Laboratory Tests**: All included cases underwent laboratory tests for complete blood count, blood urea, serum creatinine, AST, ALT, ALP, and serum uric acid, urine for proteinuria by dipstick test, these investigations required for identification of severe preeclampsia.

**Blood sample:**

One milliliter of blood for estimation of fasting blood sugar to exclude gestational diabetes.

Two milliliters of venous blood collected into EDTA tubes and analyzed using automated analyzer "ABX Micros ES 60 hematology analyzer, Horiba, France".

The ranges of the reference intervals as provided by manufacturer were as follows:

- ✓ Mean platelet volume (MPV): 6.90-10.6 fL
- ✓ Platelet (PLT): 155-366×$10^3$/µL,
- ✓ Plateletcrit= platelet count x MPV / 10000 (PCT): 0.21-0.35 %
- ✓ Platelet distribution width (PDW): 16-17.2 %

**Urinary sample:**

Urine collected for performing urinary protein dipstick to estimate the number of protein pluses.

### 2.9. Statistical analysis

All data were introduced into Microsoft Excel 16 and statistical analysis were conducted using IBM-SPSS (USA Chicago) and data were presented in the form of counts, percentage, mean, standard deviation (SD), minimum (Min) and maximum (Max) and presented in the form of tables, charts, or graphs.

Testing of the level of significance of the categorical data was conducted using Chi square or Fisher exact test while continuous variables were tested using student t test or Mann Whitney u test when appropriate. Receiver operator characteristics curve was used to estimate the best cutoff points (after running of Yoden j index test) at which estimation of the area under the curve (AUC), sensitivity (SN), specificity (SP) positive predictive value (PPV), negative predictive value (NPV), accuracy of the test (Acc) and relative risk of each variable. P value less than 0.05 considered statistically significant.

***Chapter three***

***Results***

## 3. RESULTS

The study included 300 participants, 150 cases of preeclampsia (75 cases of severe and 75 cases of mild preeclampsia) along with 150 cases as control.

The age distribution among the groups showed that participants aged 20-30 years constituted the largest proportion in each group, with 45.3% in both the severe and mild preeclampsia groups, and 36.7% in the control group. Those over 30 years of age represented 49.3% of the severe group, 46.7% of the mild group, and 56% of the control group. However, these age distributions did not differ significantly (P=0.596). The mean ages were 29.76±6.71, 28.96±6.97, and 30.49±6.85 years for the severe, mild, and control groups, respectively, which was also not statistically significant (P=0.281).

Gestational age, measured in weeks, was comparable across all groups, with means of 35.88±2.63, 35.83±2.56, and 35.63±2.55 for severe, mild, and control groups, respectively, yielding no significant difference (P=0.754).

Regarding parity, the severe preeclampsia group had 48% primiparity, 41.3% multiparity, and 10.7% grand-multiparity. The mild preeclampsia group had 41.3% primiparous, 50.7% multiparous,

and 8% grand-multiparous women. The control group reported 41.3% primiparous, 44.7% multiparous, and 14% grand-multiparous cases. These differences were not statistically significant (P=0.565).

Body Mass Index (BMI) categories showed that the majority of participants in the mild preeclampsia group and the control group fell into the 18.5-24.9 kg/m^2 range, accounting for 48% and 51.3% respectively, while the severe group had a higher percentage in the 25-29.9 kg/m^2 range (41.3%). The proportions of underweight (BMI <18.5) and obese (BMI ≥30) individuals were similar across all groups, with no significant difference in the mean BMI (P=0.24 for BMI categories and P=0.549 for mean BMI), where the means were 24.58±4.32, 24.5±3.81, and 24.04±3.96 kg/m^2 for the severe, mild, and control groups, respectively.

**Table 3-1: Distribution of demographics in the study groups:**

| Variables | | Severe | Mild | Control | P value |
|---|---|---|---|---|---|
| | | No. (%) | No. (%) | No. (%) | |
| Age | <20 | 4 (5.3) | 6 (8) | 11 (7.3) | 0.596 |
| | 20-30 | 34 (45.3) | 34 (45.3) | 55 (36.7) | |
| | >30 | 37 (49.3) | 35 (46.7) | 84 (56) | |
| | Mean ±SD | 29.76 ±6.71 | 28.96 ±6.97 | 30.49 ±6.85 | 0.281 |
| Gestational age | Mean ±SD | 35.88 ±2.63 | 35.83 ±2.56 | 35.63 ±2.55 | 0.754 |
| Parity | Primiparity | 36 (48) | 31 (41.3) | 62 (41.3) | 0.565 |
| | Multiparity | 31 (41.3) | 38 (50.7) | 67 (44.7) | |
| | Grand-multiparity | 8 (10.7) | 6 (8) | 21 (14) | |
| BMI | <18.5 | 8 (10.7) | 3 (4) | 15 (10) | 0.240 |
| | 18.5-24.9 | 27 (36) | 36 (48) | 77 (51.3) | |
| | 25-29.9 | 31 (41.3) | 29 (38.7) | 47 (31.3) | |
| | ≥30 | 9 (12) | 7 (9.3) | 11 (7.3) | |
| | Mean ±SD | 24.58 ±4.32 | 24.5 ±3.81 | 24.04 ±3.96 | 0.549 |

The average systolic blood pressure was significantly higher in the severe preeclampsia group (184.61±15.04 mmHg) compared to the mild preeclampsia group (149.49±5.47 mmHg) and the control group (118.15±7.55 mmHg), with a P value of less than 0.0001. This indicates a clear distinction in systolic blood pressure values among the groups, with the severe group displaying markedly elevated levels.

Similarly, the average diastolic blood pressure in the severe preeclampsia group was (126.83±10.81 mmHg), which was significantly higher than that in the mild preeclampsia group (99.65±6.24 mmHg) and the control group (72.47±7.45 mmHg), also with a P value of less than 0.0001.

The results demonstrate that blood pressure measurements, both systolic and diastolic, are significantly associated with the severity of preeclampsia. These findings support the use of SBP and DBP as reliable severity markers in the assessment of preeclamptic cases.

**Table 3-2: Distribution of blood pressure measurement among study groups:**

| Variables | Severe | Mild | Control | P value |
|---|---|---|---|---|
| | Mean ±SD | Mean ±SD | Mean ±SD | |
| SBP | 184.61 ±15.04 | 149.49 ±5.47 | 118.15 ±7.55 | **<0.0001** |
| DBP | 126.83 ±10.81 | 99.65 ±6.24 | 72.47 ±7.45 | **<0.0001** |

Liver enzymes showed a remarkable elevation in the severe preeclampsia group, with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels averaging 323.95±111.48 U/L and 316.6±118.69 U/L, respectively. These levels were significantly higher than those in the mild

preeclampsia group (19.16±4.48 U/L for ALT and 19.15±4.47 U/L for AST) and the control group (19.25±4.37 U/L for ALT and 19.17±4.84 U/L for AST), with P values of less than 0.0001 for comparisons between severe vs. mild (P1) and severe vs. control (P2). However, there was no significant difference between the mild preeclampsia group and the control group for these liver enzymes (P3=0.999).

Alkaline phosphatase (ALP) levels were also elevated in the severe group (124.65±3.26 U/L) compared to the mild (19.76±5.47 U/L) and control groups (21.09±5.79 U/L), with P values of less than 0.0001 when comparing severe to both mild and control groups. The difference between the mild and control groups was not significant (P3=0.215).

Uric acid levels were also elevated in the severe group (8.6 ±1.2 mg/dl) compared to the mild (7.4 ±2.1 mg/dl) and control groups (6.7 ±1.9 mg/dl), with P values of less than 0.0001 when comparing severe to both mild and control groups. The difference between the mild and control groups was also significant (P3<0.0001).

**Table 3-3: Distribution of investigations among study groups:**

| Variables | Severe | Mild | Control | P value | | |
|---|---|---|---|---|---|---|
| | No. (%) | No. (%) | No. (%) | P1 | P2 | P3 |
| ALT | 323.95 ±111.48 | 19.16 ±4.48 | 19.25 ±4.37 | **<0.0001** | **<0.0001** | 0.999 |
| AST | 316.6 ±118.69 | 19.15 ±4.47 | 19.17 ±4.84 | **<0.0001** | **<0.0001** | 0.999 |
| ALP | 124.65 ±3.26 | 19.76 ±5.47 | 21.09 ±5.79 | **<0.0001** | **<0.0001** | 0.215 |
| Uric acid | 8.6 ±1.2 | 7.4 ±2.1 | 6.7 ±1.9 | **<0.0001** | **<0.0001** | **<0.0001** |
| **P1**= Sever Vs. Mild; **P2**= Severe Vs, Control; **P3**= Mild Vs. Control | | | | | | |

Platelet count was lower in the severe preeclampsia group (187.63±37.26 x $10^9$/L) compared to the mild group (208.44±21.65 x $10^9$/L) and the control group (247.17±50.51 x $10^9$/L), with P values of less than 0.0001 for all comparisons.

Regarding platelet indices, mean platelet volume (MPV) was highest in the severe group (9.83±0.62 fL) compared to the mild (9.03±0.67 fL) and control groups (8.11±0.51 fL), with significant differences noted (P<0.0001). Platelet distribution width (PDW) and plateletcrit (PCT) followed a similar trend, with the severe group having higher values (16.11±0.99% for PDW and 0.2±0.01% for PCT) than the mild and control groups, again with P values of less than 0.0001 for comparisons between severe vs. mild and severe vs. control. However, there was no significant difference for PCT when comparing the mild vs. control groups (P3=0.699).

**Table 3-4: Distribution of the platelet indices among study groups:**

| Variables | Severe | Mild | Control | P value | | |
|---|---|---|---|---|---|---|
| | No. (%) | No. (%) | No. (%) | P1 | P2 | P3 |
| Platelet count | 187.63 ±37.26 | 208.44 ±21.65 | 247.17 ±50.51 | **<0.0001** | **<0.0001** | **<0.0001** |
| MPV | 9.83 ±0.62 | 9.03 ±0.67 | 8.11 ±0.51 | **<0.0001** | **<0.0001** | **<0.0001** |
| PDW | 16.11 ±0.99 | 14.58 ±1.01 | 12.62 ±0.92 | **<0.0001** | **<0.0001** | **<0.0001** |
| PCT | 0.2 ±0.01 | 0.22 ±0.01 | 0.23 ±0.01 | **<0.0001** | **<0.0001** | 0.699 |
| **P1**= Sever Vs. Mild; **P2**= Severe Vs, Control; **P3**= Mild Vs. Control | | | | | | |

The correlation between platelet indices and blood pressure levels, the study demonstrates statistically significant relationships as evidenced by the calculated R values and P values.

For platelet count, there was a moderate negative correlation with both systolic blood pressure (SBP) (R=-0.495) and diastolic blood pressure (DBP) (R=-0.489), with highly significant P values (<0.0001), indicating that higher blood pressure is associated with lower platelet counts, though they are still in the normal range.

Mean Platelet Volume (MPV) showed a strong positive correlation with SBP (R=0.732) and DBP (R=0.72), both with P values of less than 0.0001. This suggests that as the blood pressure increases, the MPV also tends to increase.

Platelet Distribution Width (PDW) also displayed a strong positive correlation with both SBP (R=0.789) and DBP (R=0.783), with P values less than 0.0001, indicating a significant association between higher PDW and increased blood pressure levels.

Plateletcrit (PCT) showed a moderate negative correlation with SBP (R=-0.596) and DBP (R=-0.563), with P values less than 0.0001, suggesting that higher blood pressure levels might be associated with lower PCT values.

These results suggest that in preeclamptic patients, platelet count and PCT decrease as blood pressure rises, while MPV and PDW increase, all with strong statistical significance. This underlines the potential of platelet indices to serve as informative markers for the severity of hypertension in preeclampsia.

**Table 3-5: Correlation analysis:**

| Correlations | SBP | | DBP | |
|---|---|---|---|---|
| | R value | P value | R value | P value |
| Platelet count | -0.495 | **<0.0001** | -0.489 | **<0.0001** |
| MPV | 0.732 | **<0.0001** | 0.72 | **<0.0001** |
| PDW | 0.789 | **<0.0001** | 0.783 | **<0.0001** |
| PCT | -0.596 | **<0.0001** | -0.563 | **<0.0001** |

The area under the curve (AUC) for Mean Platelet Volume (MPV) was 0.95, indicating excellent discriminative ability. The optimal cutoff point for MPV was determined to be greater than or equal to 9.15 fL, with a high sensitivity of 81.3% for detecting severe preeclampsia, and a specificity of 85.8%, meaning that it correctly identifies those without the condition as well.

Platelet Distribution Width (PDW) had an AUC of 0.926, also showing strong discriminative power. The established cutoff point for PDW was greater than or equal to 14.75%, with a sensitivity of 92%, which is the proportion of true positives identified, and a specificity of 86.7%.

Plateletcrit (PCT) demonstrated an AUC of 0.945, indicating excellent predictive capability. The cutoff for PCT was determined to be less than or equal to 0.205%, with a sensitivity of 70.7% and a particularly high specificity of 94.7%, indicating it is very effective at correctly identifying individuals without the disease.

The positive predictive value (PPV) and negative predictive value (NPV) for each index were also noteworthy. MPV had a PPV of 65.6%, meaning that when the test is positive, there is a 65.6% probability that the individual truly has severe preeclampsia. Its NPV was 93.2%, indicating a high probability that a negative test corresponds to an absence of severe preeclampsia. PDW showed a PPV of 69.7% and an NPV of 97%, while PCT had a PPV of 81.5% and an NPV of 90.6%.

Overall accuracy, which measures the proportion of true results (both true positives and true negatives) in the population, was high for all indices: 84.7% for MPV, 88% for PDW, and 88.7% for PCT.

These findings suggest that MPV, PDW, and PCT are highly effective indices for predicting severe preeclampsia, with MPV and PDW being particularly sensitive and PCT being notably specific.

**Table 3-6: Interpretation of ROC curve analysis for platelet indices in prediction of severe preeclampsia:**

| Parameter | Severe preeclampsia | | |
|---|---|---|---|
| | MPV | PDW | PCT |
| Area under the curve | 0.95 | 0.926 | 0.945 |

| Cutoff point | ≥9.15 | ≥14.75 | ≤0.205 |
|---|---|---|---|
| Sensitivity | 81.3 | 92 | 70.7 |
| Specificity | 85.8 | 86.7 | 94.7 |
| Positive predictive value | 65.6 | 69.7 | 81.5 |
| Negative predictive value | 93.2 | 97 | 90.6 |
| Accuracy | 84.7 | 88 | 88.7 |

The area under the curve (AUC) for Mean Platelet Volume (MPV) was 0.846, signifying a good ability to distinguish between cases with and without mild preeclampsia. The cutoff point for MPV was set at a value greater than or equal to 8.35 fL, with a sensitivity of 77.3% for correctly identifying true positives, and a specificity of 68% for correctly identifying true negatives.

Platelet Distribution Width (PDW) had an AUC of 0.919, indicating strong discriminative power. PDW's cutoff point was determined to be greater than or equal to 13.55%, and it showed a sensitivity of 78.7% along with a specificity of 78%.

Plateletcrit (PCT) presented an AUC of 0.517, which suggests a poor ability to discriminate between cases with mild preeclampsia and those without. The cutoff for PCT was determined to be less than or equal to 0.215%, with a low sensitivity of 29.3% and a specificity of 76.7%.

In terms of predictive values, MPV had a positive predictive value (PPV) of 54.7%, indicating the probability that subjects with a positive screening test indeed have mild preeclampsia. The negative predictive value (NPV) was 85.7%, suggesting that when the test is negative, subjects are likely to be without the condition. PDW demonstrated a PPV of 64.1% and an NPV of 88%, while PCT had a PPV of 38.6% and an NPV of 68.5%.

The overall accuracy of the tests, which indicates the proportion of true positive and true negative results, was 71.1% for MPV, 78.2% for PDW, and 60.9% for PCT.

These results imply that while MPV and PDW may be reasonably predictive for mild preeclampsia, their accuracy is less than that for severe cases. PCT, with an AUC close to 0.5, does not appear to be a reliable marker for mild preeclampsia.

**Table 3-7: Interpretation of ROC curve analysis for platelet indices in prediction of mild preeclampsia.**

| **Parameter** | **Mild preeclampsia** | | |
|---|---|---|---|
| | **MPV** | **PDW** | **PCT** |
| Area under the curve | 0.846 | 0.919 | 0.517 |
| Cutoff point | ≥8.35 | ≥13.55 | ≤0.215 |
| Sensitivity | 77.3 | 78.7 | 29.3 |
| Specificity | 68 | 78 | 76.7 |
| Positive predictive value | 54.7 | 64.1 | 38.6 |
| Negative predictive value | 85.7 | 88 | 68.5 |
| Accuracy | 71.1 | 78.2 | 60.9 |

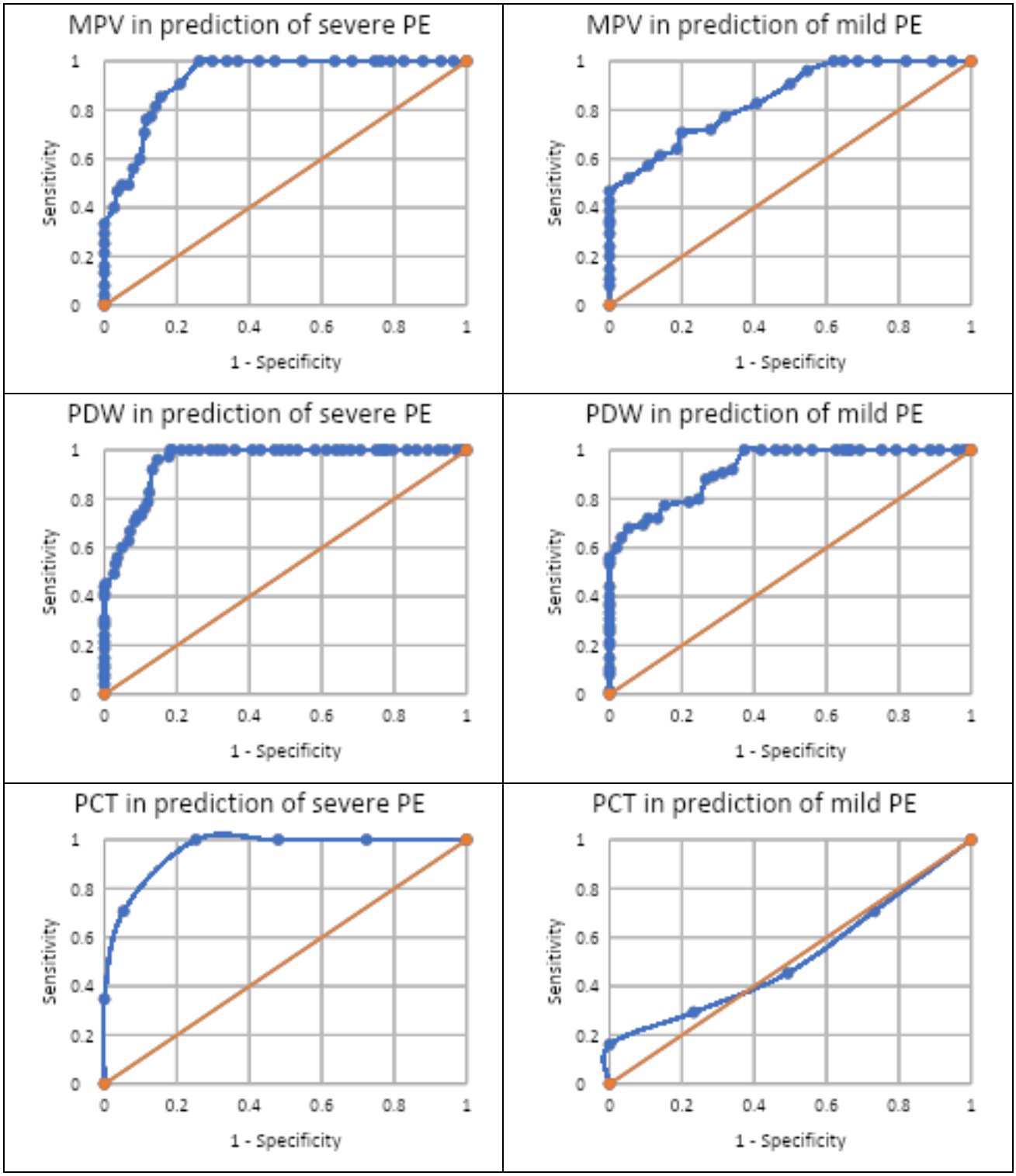


**Figure 3-1: Receiver operator characteristic curves of platelet indices in prediction of severe and mild preeclampsia.**

***Chapter four***

***Discussion***

## 4. DISCUSSION

Regarding age distribution, gestational age, parity, and BMI among preeclamptic cases and controls, the lack of significant differences in age distribution, with the largest proportion of participants aged 20-30 years across severe and mild preeclampsia groups and controls, aligns with previous studies indicating that preeclampsia can occur across a wide age range. However, some studies suggest that the risk of hypertensive disorders, including preeclampsia, may increase with

maternal age, particularly in women over 35 years old, due to age-related physiological changes and an increased likelihood of underlying health conditions Xiaoli et al [72].

The comparable gestational ages at the time of the study among all groups, with no significant differences, reinforce the clinical understanding of preeclampsia as a disorder that typically manifests after 20 weeks of gestation.

Regarding parity, the distribution among the groups suggests that preeclampsia can affect both primiparous and multiparous women, although first-time pregnancies are often considered a risk factor for the condition. The parity distribution in the current study, showing no significant differences, may suggest that while primiparity is a recognized risk factor, preeclampsia also significantly affects women with previous pregnancies, underscoring the complexity of its risk factors, as suggested by Hamzah et al[73].

The BMI findings from the current study, indicating no significant differences in mean BMI across the groups and a higher percentage of participants in the severe preeclampsia group falling into the 25-29.9 $kg/m^2$ range, add to the mixed evidence regarding the role of BMI in preeclampsia. While obesity is a known risk factor for preeclampsia, the non-significant difference in mean BMI in the current study suggests that BMI alone may not be a sufficient predictor of preeclampsia severity. This aligns with some research indicating that while there is an association between higher BMI and increased risk of preeclampsia, the relationship may be influenced by other factors, such as genetic predisposition, lifestyle, and underlying health conditions, as suggested by Lewandowska et al[74] and Xiu-Jie et al[75].

The significant elevation in liver enzymes (ALT and AST) and alterations in platelet indices observed in the severe preeclampsia group, as compared to the mild preeclampsia and control groups, are indicative of the systemic nature of severe preeclampsia and its impact on hepatic function and platelet dynamics. These findings are consistent with the known pathophysiology of severe preeclampsia, which involves endothelial dysfunction, oxidative stress, and an inflammatory response leading to multiorgan involvement, including the liver.

Although the current study did not include cases of low platelet count (an essential criterion for the full picture of HELLP syndrome), yet cases of elevated liver enzymes were found.

Elevated liver enzymes in severe preeclampsia, particularly AST and ALT, suggest hepatic involvement which can range from mild hepatic dysfunction (without HELLP) to more severe complications like the HELLP syndrome. This hepatic involvement is attributed to endothelial damage and microangiopathic processes, leading to hepatic ischemia and necrosis, thereby elevating liver enzymes. Such elevations are significant markers of disease severity and can help in differentiating between mild and severe forms of preeclampsia, aiding in the management and prognosis of the condition, as suggested by Greiner et al[76].

The current study found that the MPV increase in cases of severe preeclampsia, a finding that found to be consistent with the studies of Bulbul et al[77], and Walle et al[63] in their systematic review and meta-analysis.

The alteration in platelet indices, including lower platelet count and higher mean platelet volume (MPV) in severe preeclampsia, reflects the increased consumption and destruction of platelets, which is characteristic of severe preeclamptic conditions. The elevated MPV indicates the release of larger, younger platelets from the bone marrow in response to increased platelet turnover, which is a compensatory mechanism in response to platelet consumption in the microcirculation as suggested by Saran et al[78]. This phenomenon is also observed in other conditions associated with increased platelet activation and consumption, such as the HELLP syndrome.

Platelet distribution width is a marker of platelet variability and activation. The significant increase in PDW among severe preeclampsia patients compared to mild and control groups suggests that there is greater platelet activation and variability in severe cases. This could be indicative of a heightened inflammatory and thrombotic state associated with severe preeclampsia.

The meta-analysis conducted by Abass et al[79] highlighted that PDW levels were significantly higher in preeclampsia patients compared to healthy pregnant controls, with even more pronounced elevations in severe versus mild cases of preeclampsia. This supports the notion that PDW could serve as a promising biomarker for detecting preeclampsia and assessing its severity, reflecting the heightened inflammatory and thrombotic state associated with severe preeclampsia.

Furthermore, Mohapatra et al[80] found that this elevation could be significantly found in cases of preeclampsia even in the absence of thrombocytopenia (which was similar to the current study).

The current study showed that low PCT level were associated with cases of severe preeclampsia. While cases of mild and control were not different regarding the level of PCT.

Similar result found by Mohapatra et al[80] and Temur et al[81]. The lack of significant difference in PCT between mild preeclampsia and control groups in the current study aligns with some of the previous research, suggesting that while PCT may alter in preeclampsia, its sensitivity as a marker for mild forms of the condition might be limited. This is further supported by the study conducted by Elbasuony et al [82], which found significant changes in MPV and PDW but not in PCT, indicating that not all platelet indices are equally predictive of preeclampsia severity.

The correlation analysis unveiled interesting patterns. It demonstrated a moderate negative association between platelet count and both systolic and diastolic blood pressure (SBP and DBP), while revealing strong positive correlations between mean platelet volume (MPV) and platelet distribution width (PDW) with blood pressure. Additionally, a strong positive correlation was found between MPV, PDW, and both SBP and DBP, while plateletcrit (PCT) displayed a moderate negative correlation with blood pressure levels. These findings collectively suggest that as blood pressure increases, there might be a reduction in platelet count, potentially due to platelet consumption in the formation of microthrombi in the vasculature—a common feature in severe preeclampsia.

These correlations underline the complex interplay between hypertension and platelet dynamics in preeclampsia. The alterations in platelet indices not only reflect the severity of hypertension but also suggest an increased risk of coagulopathy in preeclamptic patients. These findings emphasize the potential utility of platelet indices as non-invasive, easily measurable markers that could assist in monitoring the progression and severity of preeclampsia, contributing to better patient management and outcomes.

Umezuluike et al[83] found significant correlation of platelet indices with both blood pressure and adverse maternal and neonatal outcomes in preeclamptic patients.

The findings from the presented study indicate that MPV, with an AUC of 0.95 and a cutoff point of ≥9.15 fL, and PDW, with an AUC of 0.926 and a cutoff point of ≥14.75%, are reliable markers in predicting severe preeclampsia. These results are consistent with several previous studies, Reddy et al[84] found that cases of severe preeclampsia associated with 80% sensitivity and 75% specificity at cutoff point of >10.95 fl for MPV and 66% and 62% sensitivity and specificity respectively for PDW at cutoff point of >17.75%, these differences may be attributed in difference in the cutoff point selected or difference in laboratory calibrations, but it shares the same concept that these markers increased in severe preeclampsia patients. While Ye et al[85] in their meta-analysis found that MPV has a moderate predictive and diagnostic value for PE, particularly in diagnosing after 20 weeks of gestation. The diagnostic accuracy is higher when the MPV cut-off falls between 9 and 10 fl. To note that the study of Ye et al[85] based the ability of early pregnancy measurement of MPV in diagnosis of later on preeclampsia, while the current study investigated the role of these markers in prediction of severe features of preeclampsia.

The predictive ability of PCT was lower than that of MPV and PDW in the current study. To note that this was not investigated by previous studies.

The current study did not find significant predictive ability of these markers in prediction of mild preeclampsia. Similarly found by Reddy et al[84] and Kim et al[86].

***Chapter five***

***Conclusion & Recommendations***

## 5. Conclusion and Recommendations

### 5.1. Conclusion

- Platelet indices, especially MPV and PDW, show promise as reliable markers for assessing preeclampsia severity, correlating strongly with blood pressure levels.
- MPV, PDW, and PCT exhibit varying effectiveness in predicting preeclampsia severity. MPV and PDW are valuable for severe cases, while PCT is more specific but less sensitive, especially for severe cases (MPV: Sensitivity 81.3%, Specificity 85.8%; PDW: Sensitivity 92%, Specificity 86.7%; PCT: Sensitivity 70.7%, Specificity 94.7%).
- These platelet indices can enhance early identification and management of preeclampsia severity.

### 5.2. Recommendations

- **Incorporate Platelet Indices in Preeclampsia Assessment:** Clinicians could consider incorporating MPV and PDW measurements as routine assessments for pregnant women with preeclampsia, as these indices have demonstrated strong potential in evaluating the severity of the condition.
- **Utilize Platelet Indices for Risk Stratification:** MPV and PDW can be used to stratify patients with preeclampsia into different risk categories. This stratification can aid in identifying individuals who may require more intensive monitoring and timely interventions, especially those with severe preeclampsia.
- **Further Research and Validation:** Conduct further research to validate the use of platelet indices, particularly PCT, as specific markers for severe preeclampsia. Additionally, explore the applicability of these indices in different healthcare settings and populations.
- **Education and Training:** Ensure that healthcare professionals are educated and trained in the use and interpretation of platelet indices to enhance their clinical utility in assessing preeclampsia severity.
- **Regular Monitoring:** Establish protocols for regular monitoring of platelet indices alongside traditional clinical parameters such as blood pressure, liver enzymes, and urine protein levels in preeclamptic patients to provide a more comprehensive assessment of disease progression.
- **Patient Counseling:** Inform patients about the significance of platelet indices in preeclampsia assessment and involve them in the decision-making process regarding their prenatal care and management.

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