UNIVERSITY FOR DEVELOPMENT STUDIES

COMPARATIVE ACCURACY OF BLOOD AND PLACENTAL MARKERS IN THE PREDICTION OF PREECLAMPSIA IN THE UPPER EAST REGION

MARTIN AWE AKILLA

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By

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A THESIS SUBMITTED TO THE DEPARTMENT OF BIOMEDICAL LABORATORY SCIENCES, SCHOOL OF ALLIED HEALTH SCIENCES, UNIVERSITY FOR DEVELOPMENT STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF DOCTOR OF PHILOSOPHY IN CHEMICAL PATHOLOGY

FEBRUARY, 2024

DECLARATION

Student

I hereby declare that this dissertation/thesis is the result of my own original work and that no part of it has been presented for another degree in this University or elsewhere:

Candidate's Signature: …… ……. Date: 06/08/2024

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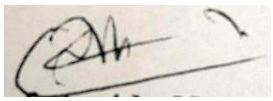
Supervisors

I, at this moment, declare that the preparation and presentation of the dissertation/thesis were supervised following the guidelines on supervision of dissertation/thesis by the University for Development Studies.

Principal Supervisor's



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ABSTRACT

Preeclampsia (PE) remains a significant global concern for maternal-foetus health, particularly in low to middle-income countries. Identifying biomarkers for early PE diagnosis is paramount for effective prevention and management. This case-control study, conducted at Bolgatanga Regional Hospital, involved 250 pregnant women (PE=100 and controls=150), aged 18 to 41 years, spanning January to December 2022. Fasting venous blood samples and placental tissues were collected at delivery and analyzed for neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR). Additionally, placental and serum levels of total cholesterol (TCHOL), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (CRT), urea, blood urea nitrogen (BUN), and uric acid (UA) were assessed. Furthermore, placental malondialdehyde (MDA), catalase activity (CAT), total peroxide activity (TP), total antioxidant capacity (TAC), and oxidative stress index (OSI) were estimated. All analyses were conducted using fully automated haematology and biochemistry analyzers. The findings revealed elevated levels of both NLR and MLR in PE cases, demonstrating significant predictive capacity for PE with area under the curve (AUC) values of 0.85 and 0.89, respectively. Furthermore, PE was associated with higher placental levels of MDA and OSI, along with reduced total TAC and CAT activities. Additionally, placental levels of MDA, TAC, CAT, and TP emerged as significant predictors of PE, with respective AUCs of 0.68, 0.76, 1.00, and 0.70. Furthermore, elevated placental levels of CRT and UA were observed in PE cases. On the contrary, PE was associated with higher serum levels of TCHOL, LDL cholesterol, AST, ALT, urea, CRT, BUN, and UA, while serum HDL levels were lower. Notably, in predicting PE, placental CRT exhibited significant potential with an AUC of 0.95 at $P<0.001$. Regarding serum markers, the performances were as follows (AUC, P-value): HDL (0.68, 0.037), LDL (0.86, <0.001), AST (0.93, <0.001), ALT (0.95, <0.001), urea (0.72, 0.004), CRT (0.77, <0.001), BUN (0.72, 0.006), and uric acid (0.76, 0.002). Placental catalase activity emerges as the strongest predictor of preeclampsia. However, assessing placental catalase activity may pose challenges due to the more invasive, time-consuming, and costly sampling procedure. Consequently, less invasive and more cost-effective markers, such as red cell indices or serum-based markers, are preferred alternatives.

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DEDICATION

This work is dedicated with all my love to my son, Rodney Awuvere Akilla, and my daughter, Mary-Magdalene Wedaga Akilla. With deep affection for my late father, Mr. John Awuchiragani Akilla.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynaecologists.
ALT	Alanine Aminotransferase.
AOPP	Advanced Oxidation Protein Products.
aPTT	Activated Partial Thromboplastin Time.
AST	Aspartate Aminotransferase.
ATM	Ataxia-Telangiectasia Mutated.
ATP	Adenosine Triphosphate.
BHT	Butylated Hydroxytoluene.
BLR	Basophil to Lymphocyte Ratio.
BMI	Body Mass Index.
BPP	Biophysical Profile.
BUN	Blood Urea Nitrogen.
CAD	Coronary Artery Disease.
CAPs	Carboxyalkyl Pyrroles.
CAT	Catalase.
CBC	Complete Blood Count.
Cr	Creatinine.
CRT	Creatinine.
CT	Computed Tomography.
CTV	Villous Cytrophoblasts.
DBP	Diastolic Blood Pressure.
DIC	Disseminated Intravascular Coagulation.
DNA	Deoxyribonucleic Acid
ECs	Endothelial Cells.
EDTA	Ethylenediaminetetraacetic Acid
eGFR	estimated Glomerular Filtration Rate.
ELR	Eosinophil to Lymphocyte Ratio.
EVT	Extravillous Trophoblasts.
FATPs	Fatty Acid Transport Proteins.
GFR	Glomerular Filtration Rate.

GK	Glycerol Kinase.
GOD	Glucose Oxidase.
GPO	Phosphate Oxidase.
GPx	Glutathione Peroxidase.
GR	Glutathione Reductase.
hCG	Human Chorionic Gonadotrophin Hormone.
HDL	Decreased High-Density Lipoprotein.
HDL-C	HDL-Cholesterol.
HELLP Syndrome	Haemolysis, Elevated Liver enzymes, and Low Platelet count.
HIF-1	Hypoxia-Inducible Factor-1
hPL	Human Placental Lactogen.
HPLC	High-performance liquid chromatography
I/R	Ischaemia/Reperfusion.
IL-6	Interleukin-6.
IUGR	Intrauterine Growth Restriction.
LBW	Low Birth Weight.
LDH	Lactate Dehydrogenase.
LDL-C	Low Density Lipoprotein Cholesterol.
MCH	Mean Corpuscular Haemoglobin.
MCHC	Mean Corpuscular Haemoglobin Concentration.
MCV	Mean Corpuscular Volume.
MDRD	Modification of Diet in Renal Disease.
MLR	Monocyte to lymphocyte Ratio.
MMPs	Metalloproteinases.
MRI	Magnetic Resonance Imaging.
mRNA	Messenger RNA
NICU	Neonatal Intensive Care Unit.
NLR	Neutrophil to lymphocyte Ratio.
NO	Nitric Oxide.
NP	Normotensive Pregnancy.
NST	Non-Stress Test.
pALT	Placental Alanine Aminotransferase.

pAST	Placental Aspartate Aminotransferase.
PBS	Phosphate Buffer Saline.
pCAT	Placental Catalase.
pCRT	Placental Creatinine.
PE	Preeclampsia.
pGH	Placental Growth Hormone.
PlGF	Placental Growth Factor.
pMDA	Placental
pMDA	Placental Malondialdehyde.
POD	Peroxidase.
pOSI	Placental Oxidative Stress Index.
pOSI	Placental Oxidative Stress Index.
PT	Prothrombin Time.
pTAC	Placental Total Antioxidant Capacity.
pTAC	Placental Total Antioxidant Capacity>
pTRIG	Placental Triglycerides.
pUA	Placental **U**ric Acid.
pVLDL	Placental Very Low-Density Lipoprotein
RAAS	Renin-Angiotensin-Aldosterone System**.**
RBC	Red Blood Cell.
RBP-4	Retinol-Binding Protein-4**.**
RNA	Ribonucleic Acid
ROC	Receiver Operator Characteristic.
ROS	Reactive Oxygen Species.
SBP	Systolic Blood Pressure.
SCT	Syncytiotrophoblast.
sEng	Soluble Endoglin.
sFlt-1	soluble fms-like tyrosine kinase-1.
SLE	Systemic Lupus Erythematosus.
SOD	Superoxide Dismutase.
SPSS	Statistical Package for the Social Sciences
STBs	Syncytiotrophoblasts.

TBA	Thiobarbituric Acid.
TBARS	Thiobarbituric Acid Reacting Substances.
TGF-β1	Transforming Growth Factor Beta 1
TLRs	Toll-Like Receptors.
TNF-α	Tumor Necrosis Factor-Alpha.
UA	**U**ric Acid.
VEGF	Vascular Endothelial Growth Factor.
VLDL-C	Very Low-Density Lipoprotein Cholesterol.
VUE	Villitis of Unknown Aetiology
WBC	White Blood Cell.
4-HNE	4-hydroxynonenal.
8-OHdG	8-Hydroxy-2'-deoxyguanosine.

Chapter 1

INTRODUCTION

1.1 GENERAL INTRODUCTION

Preeclampsia stands as a critical global health issue, affecting maternal health across the globe. The disease affects between 2% and 8% of births globally and is a major cause of neonatal and maternal death and morbidity (Shih et al., 2016). This condition's complexity lies in its multifactorial nature, involving genetic, immunological, and environmental influences (Pennington et al., 2012). Despite being extensively studied; its precise aetiology remains elusive. The condition is marked by the onset of high blood pressure and is often accompanied by symptoms of damage to several organ systems, especially the kidneys and liver. Its underlying mechanisms are often linked to abnormal placental development, vascular dysfunction, and inflammation, resulting in endothelial damage and subsequent clinical symptoms. This disease typically manifests itself during the 20th week of pregnancy and if left untreated it can cause major complications for both the foetus and the mother.

The underlying cause of preeclampsia remains largely unknown, often described as a 'disease of theories' (Ekman, 2009; Lindheimer & Katz, 1981). Pre-existing conditions significantly escalate the risk: insulin-dependent diabetes increases the likelihood nearly four-fold if present before pregnancy (Catov et al., 2007; Padmanabhan et al., 2017), however, women who develop preeclampsia are at a higher risk of having chronic hypertension (Chen et al., 2017; Shen et al., 2017). As a single organ connecting the mother and foetus, the placenta facilitates the exchange of gases, nutrition, waste, heat, hormones, and regulatory molecules, all of which are essential to the development of a healthy child. Extremely small or premature babies face increased risks of mortality and various morbidities, notably neurological, respiratory, and gastrointestinal diseases (Tan et al., 2014), where placental

characteristics determine foetus development and future disease patterns. In low- and middle-income nations, where there may be limited access to healthcare and prenatal care, preeclampsia is more prevalent. In some areas, the prevalence can exceed 10% of pregnancies. Among these countries, prevalent rates are reported as; Zimbabwe (58%), China (38%), Cameroon (37.4%), Thailand (34%), Mauritius (34%), Réunion (31%), Guadeloupe (31%), Turkey (29%), and India (26%) (Firoz et al., 2011; Ratsiatosika et al., 2019).

Preeclampsia can impact differently in Sub-Saharan Africa depending on regional and cultural factors. In Ghana, a country in West Africa, preeclampsia is a major contributor to maternal health issues. Research shows that Ghanaian women experience varying levels of susceptibility and outcomes (Ababio et al., 2019; Amidu et al., 2021; Yeboah et al., 2018), highlighting regional disparities in healthcare access, genetic predispositions, and sociodemographic influences.

In Ghana's Upper East Region, certain factors can influence the onset and severity of preeclampsia. The Upper East Region, which is characterized by a unique sociodemographic and healthcare landscape, might exhibit distinct patterns in preeclampsia prevalence and management. Challenges related to access to quality healthcare, nutritional status, and community-specific practices might impact the outcomes of pregnant women facing this condition. However, within the discipline of obstetrics and gynaecology, preeclampsia stands as a significant focus area. Efforts to understand its pathophysiology, early prediction, and effective management are ongoing. Its elusive nature in terms of diagnosis and prediction prompts a continuous quest for reliable biomarkers, including blood cell indices and markers of oxidative stress, which is crucial.

Blood cell indices and oxidative stress markers have drawn attention recently as viable options to improve the precision of preeclampsia diagnosis.

In an effort to refute current beliefs and evaluate the diagnostic utility of blood cell indices and oxidative stress markers in the context of this multifaceted disease, this study investigates their potential for preeclampsia prediction and diagnosis. The hypothesis underpinning this investigation challenges the prevailing belief by positing that these markers do not possess predictive potential in diagnosing preeclampsia. Furthermore, it questions the assumed associations between dyslipidaemia, renal impairment, hepatic injury, and preeclampsia among pregnant Ghanaian women, aiming to offer clarity on these interrelationships. These markers offer potential diagnostic avenues, aiding in timely intervention and risk assessment for pregnant women, particularly in regions like the Upper East of Ghana, where resources may be limited.

1.2 PROBLEM STATEMENT:

In Sub-Saharan Africa, the impact of preeclampsia may vary based on cultural and geographical differences. Within Ghana, a West African nation, preeclampsia contributes significantly to maternal health challenges. Studies indicate variations in susceptibility and outcomes among Ghanaian women (Ababio et al., 2019; Amidu et al., 2021; Yeboah et al., 2018), reflecting regional disparities in healthcare access, genetic predispositions, and sociodemographic factors. Preeclampsia continues to rank among the world's most common causes of illness and death for expectant mothers and their babies. Despite advancements in prenatal care, accurately predicting and early detecting preeclampsia remain major challenges for healthcare providers. The current markers used for predicting preeclampsia, such as blood

pressure and proteinuria, lack sufficient sensitivity and specificity, often leading to late diagnosis and suboptimal management of the condition.

Furthermore, there is ambiguity regarding the most accurate predictive markers for preeclampsia. Both blood and placental markers have been suggested, but their comparative accuracies have not been thoroughly evaluated. This knowledge gap makes it difficult to create predictive models and preventative measures that work.

The difficulty of identifying and validating reliable biomarkers for the early identification of preeclampsia is the focus of this work.

By comparing the predictive accuracies of various blood and placental markers, this research aims to provide evidence that can enhance the current understanding and management of preeclampsia. The ultimate goal is to improve maternal and foetus outcomes by facilitating early and accurate prediction and allowing for timely and effective clinical interventions.

1.3 JUSTIFICATION OF STUDY:

In Ghana's Upper East Region, various factors may affect the incidence and severity of preeclampsia. This region, with its unique sociodemographic and healthcare characteristics, might show distinct patterns in the prevalence and management of preeclampsia. Issues such as access to quality healthcare, nutritional status, and community-specific practices could influence the outcomes for pregnant women dealing with this condition. However, within the discipline of obstetrics and gynaecology, preeclampsia stands as a significant focus area. Efforts to understand its pathophysiology, early prediction, and effective management are ongoing. Despite considerable research efforts, predicting and diagnosing preeclampsia early remains difficult due to the condition's complex pathophysiology. The study's justification stems from the urgent need to improve preeclampsia prediction and early diagnosis to lessen

its adverse consequences. The lack of accuracy in current prediction biomarkers and diagnostic instruments causes a delay in diagnosis and intervention.

Considering the elusive nature of the disease in terms of diagnosis and prediction, new reliable biomarkers that can precisely predict the development of preeclampsia, are much more needed in these circumstances. This prompts a continuous quest for reliable biomarkers, including blood cell indices and oxidative stress markers, which essentially will enable prompt and effective diagnoses of preeclampsia and treatment interventions in pregnancies.

The study aims to fill the gap in knowledge by comparing the predictive accuracies of blood and placental markers. Understanding which markers provide the most reliable predictions can significantly improve clinical outcomes by facilitating early diagnosis and intervention. In addition, this research investigates the relationship between maternal characteristics and oxidative stress as well as systemic biochemistry alterations in preeclampsia, providing a thorough understanding of its pathogenesis.

1.4 HYPOTHESIS:

NULL: We hypothesized that blood cell indices and oxidative stress markers do not have predictive potential in the diagnosis of preeclampsia. We further state that there is no association between dyslipidaemia, renal impairment, hepatic injury and preeclampsia.

ALTERNATIVE: Blood cell indices and oxidative stress markers do have predictive potential in the diagnosis of preeclampsia. We further state that there is an association between dyslipidaemia, renal impairment, hepatic injury, and preeclampsia.

1.5 AIM OF STUDY:

This research aims to evaluate the predictive accuracy of blood and placental biomarkers for the early identification of preeclampsia.

1.6 RESEARCH QUESTION:

How do maternal sociodemographic, anthropometric, obstetric, and clinical characteristics; blood cell indices (NLR and MLR); placental oxidative stress markers (MDA, TAC, CAT, TP, and OSI); and serum biochemistry markers (HDL-cholesterol, total cholesterol, LDL-cholesterol, triglycerides, VLDL-cholesterol, AST, ALT, BUN, uric acid, creatinine, and urea) predict the probability and severity of preeclampsia in the Upper East Region of Ghana, considering regional factors such as healthcare access, nutritional status, and community-specific practices?

1.7 SPECIFIC OBJECTIVES:

1. To assess the association between preeclampsia and maternal sociodemographic characteristics, anthropometric measures, obstetric history, and clinical characteristics.
2. To evaluate the predictive accuracies of blood cell indices, specifically the monocyte-to-lymphocyte ratio (MLR) and neutrophil-to-lymphocyte ratio (NLR), for preeclampsia.
3. To investigate the effect of blood pressure on placental oxidative stress markers, including total antioxidant capacity (TAC), malondialdehyde (MDA), catalase (CAT), oxidative stress index (OSI), and total peroxide (TP).

4. To determine the predictive accuracies of placental oxidative stress markers, namely total antioxidant capacity (TAC), malondialdehyde (MDA), catalase (CAT), oxidative stress index (OSI), and total peroxide (TP).
5. To compare the predictive accuracies of placental and serum biomarkers, including total cholesterol, triglycerides, HDL-chol., VLDL-chol., LDL-chol., AST, ALT, urea, BUN, uric acid, and creatinine, for preeclampsia.

1.8 SIGNIFICANCE OF THE STUDY:

The implications of identifying reliable biomarkers for preeclampsia are vast; promising earlier intervention, more targeted care strategies, and perhaps lower rates of mortality and morbidity among mothers and newborns. The findings from this research could reorient clinical practices, particularly in resource-constrained settings.

1.9 THEORETICAL/CONCEPTUAL FRAMEWORK:

This study hinges upon the theoretical framework that proposes blood cell indices and oxidative stress markers as potential diagnostic tools for preeclampsia, linking these biological markers to existing literature on the disorder's pathophysiology and diagnostic challenges.

1.10 ASSUMPTIONS/THEORETICAL LIMITATIONS:

Acknowledging potential limitations in the scope of the study is essential. The assumptions include the specificity and sensitivity of selected markers in diagnosing preeclampsia,

potential variations within the Ghanaian population, and the need for further validation in diverse settings.

1.11 Definition of Relevant Terms:

Preeclampsia: A pregnancy-related condition marked by elevated blood pressure and potential damage to other organs, usually emerging after the 20th week of pregnancy.

Blood Cell Indices: Quantitative measurements of different blood cell types, such as red blood cells, white blood cells, and platelets, are used to evaluate overall blood health and diagnose medical conditions.

Oxidative Stress Markers: Biomarkers that indicate damage to cells resulting from an imbalance between reactive molecules (oxidants) and the body's defence mechanisms (antioxidants), reflecting the levels of oxidative stress.

Chapter 2

LITERATURE REVIEW

2.1 PREECLAMPSIA

After 20 weeks of pregnancy, preeclampsia a hypertensive disorder is marked by increased blood pressure and significant proteinuria. This condition leads to high morbidity and mortality rates globally, posing a danger to the health of both the mother and the foetus.

Targeted research is crucial for improving maternal health outcomes in Sub-Saharan Africa, including Ghana, where cultural, geographic, and healthcare disparities exacerbate the impact of preeclampsia. Preeclampsia's common symptoms include severe headaches, blurred vision, and swelling of the face and hands. If untreated, these symptoms can progress to eclampsia, chronic cardiovascular diseases, and HELLP syndrome (Haemolysis, Elevated Liver Enzymes, Low Platelets), for the mother. Preterm birth, intrauterine growth restriction, and stillbirth are among the other risks that preeclampsia poses to the foetus.

In Ghana and other parts of Sub-Saharan Africa, several factors exacerbate the impact of preeclampsia. Limited access to quality prenatal care means that many cases go undiagnosed until they become severe. Cultural beliefs and practices may also delay seeking medical help, while geographical barriers such as remote and hard-to-reach areas further hinder timely healthcare access. Additionally, healthcare facilities in these regions often lack the necessary resources and trained personnel to manage preeclampsia effectively. Addressing these challenges requires a multifaceted approach.

Improving prenatal care access and quality, raising awareness in communities about the significance of early identification and intervention, and equipping healthcare facilities with the necessary tools and training are essential steps. Research dedicated to understanding the local epidemiology and management of preeclampsia can yield valuable insights, facilitating the

development of targeted interventions to significantly reduce the mortality and morbidity linked to this condition in Sub-Saharan Africa.

2.2 EPIDEMIOLOGY AND GLOBAL IMPACT OF PREECLAMPSIA.

The impact of preeclampsia extends well beyond the immediate period surrounding childbirth, affecting both the mother and the infant in significant ways. Women who have had preeclampsia are significantly more likely to suffer cardiovascular diseases in the future (Abalos et al., 2013). This includes conditions such as chronic hypertension and stroke, which can significantly impact their long-term health and quality of life.

Preeclampsia affects 5–8% of pregnancies worldwide, and so plays a substantial role in maternal and perinatal illness and mortality (Abalos et al., 2013).

Furthermore, there is an increased risk of unfavourable delivery outcomes for infants whose mothers have preeclampsia, both in the short and long term. These babies are more likely to be prematurely born, which increases the risk of preterm birth problems. They also have a higher probability of being born with a low birth weight, which is linked to several health problems at birth and in later life. Long-term health problems can include chronic diseases that last into adulthood and developmental disabilities (Adams et al., 2014; McDonald et al., 2008; von Dadelszen & Magee, 2008).

Preeclampsia is a major global health issue, with the potential to affect both maternal and foetus outcomes. Its prevalence varies around the world and can have far-reaching effects on healthcare systems and public health, which underscores the importance of effective management and long-term monitoring of both mothers and their children who have been affected by this condition.

2.2.1 Epidemiology

The incidence of preeclampsia differs worldwide, shaped by factors such as genetics, socioeconomic background, and availability of healthcare services. In wealthier nations, the rate of preeclampsia is generally lower due to advanced prenatal care and early diagnostic methods. Even in these affluent locations, pregnant women and their unborn children are nonetheless seriously at risk from this disease. Contrary, in low- and middle-income areas, especially in South Asia and Sub-Saharan Africa, the prevalence of preeclampsia is notably higher (Aftab et al., 2021).

These regions face significant challenges such as limited access to quality healthcare, inadequate prenatal care, delayed diagnosis (Ratsiatosika et al., 2019). Additionally, factors like malnutrition, infections, and lack of education further exacerbate the prevalence and severity of this disease among women.

2.2.2 Global Impact of Preeclampsia:

Preeclampsia is a prevalent disease condition that arises during pregnancy, with its prevalence rates differing across the globe. It can affect women of all races and ethnicities, but the risk factors and incidence can differ among populations.

In affluent nations, the occurrence of preeclampsia is generally lower, estimated to affect between 2% and 5% of pregnancies (Firoz et al., 2011; Goldenberg et al., 2011). This is attributed to better access to prenatal care, early detection, and management. Preeclampsia risk can be increased by several variables, such as; being a first-time mother, having a history of preeclampsia, carrying multiple gestations (such as twins or triplets), being under 20 or over 40 years old, and having certain underlying health conditions like chronic hypertension or diabetes. Preeclampsia poses significant health threats to both the mother and the foetus, contributing to elevated global rates of the disease and death. For mothers, potential complications include

eclampsia, stroke, organ failure, and long-term cardiovascular issues. For foetuses, risks encompass preterm birth, intrauterine growth restriction, and stillbirth.

2.2.2.1 Maternal Impact:

Morbidity and Mortality:

Worldwide, preeclampsia accounts for 10–15% of maternal fatalities (Abalos et al., 2013; Ghulmiyyah & Sibai, 2012). Severe cases carry significant risks for consequences such as HELLP syndrome and acute kidney or liver failure. Women who have had preeclampsia are more likely to go on to have cardiovascular disorders in the future, including hypertension, ischaemic heart disease, and stroke (Garovic & August, 2013).

2.2.2.2 Foetus Impact:

Prematurity: Preeclampsia can cause the developing foetus to have several unfavourable birth outcomes, such as lower birth weight, premature birth, and intrauterine growth restriction (IUGR) (McDonald et al., 2008). Particularly, preterm birth can result in long-term developmental difficulties and problems with the health of the newborn.

2.2.2.3 Healthcare Costs:

Preeclampsia places a significant economic burden on healthcare systems, as it often requires intensive monitoring, hospitalization, and, in severe cases, neonatal intensive care. The expenses related to managing preeclampsia, along with its potential long-term health impacts on mothers, are significant.

2.2.2.*4 Global Health Disparities:*

Preeclampsia highlights global health disparities, disproportionately impacting low- and middle-income countries where the condition is more prevalent and severe (Ratsiatosika et al., 2019). Factors such as restricted access to high-quality prenatal care, insufficient awareness, and socioeconomic challenges contribute to the higher incidence and worse outcomes in these areas.

2.2.2.5 Research and Awareness:

Preeclampsia has prompted extensive research to better understand its pathophysiology, risk factors, and management strategies. International organizations and advocacy groups are working to raise awareness and promote best practices for early detection and management. Efforts to address the global impact of preeclampsia include improved access to prenatal care, the development of diagnostic tools and preventive measures, and greater investment in maternal and neonatal healthcare services. Timely detection and effective management are crucial for alleviating the effects of preeclampsia on improving pregnancy outcomes worldwide and the health of mothers and foetuses.

2.2.3 Impact and Prevalence of Preeclampsia in Ghana

In Ghana, preeclampsia poses a significant health challenge, leading to substantial morbidity and mortality for both mothers and foetuses (Adu-Bonsaffoh et al., 2014; Dassah et al., 2019).

2.2.3.1 Prevalence of Preeclampsia in Ghana:

In Ghana, preeclampsia is a common complication during pregnancy, with studies indicating an incidence rate of about 6-8% among pregnant women (Obed, 2006). There is variability of PE prevalences across regions of Ghana. The prevalence of preeclampsia can vary significantly across different regions of Ghana. For instance, research conducted in the Greater Accra Region revealed a prevalence rate of 7.0% (Sawe et al., 2018), whereas about 7.2% is reported in the Upper East Region (Azongo et al., 2019).

2.2.3.2 Contribution to Maternal Mortality:

In Ghana, preeclampsia plays a major role in maternal mortality. It is estimated that hypertensive disorders, including preeclampsia, contribute to approximately 18-22% of maternal mortality ((GHS). 2017).

2.2.4 The Impact of Preeclampsia in Ghana:

2.2.4.1 Maternal Health:

Preeclampsia is a major contributor to maternal health problems, frequently resulting in more severe conditions such as; eclampsia, persistent hypertension, and HELLP syndrome (Agyei-Mensah, 2010; Akilla et al., 2024).

2.2.4.2 Perinatal Outcomes:

The condition has a considerable impact on perinatal outcomes, resulting in preterm delivery, low birth weight, and intrauterine growth restriction (IUGR). complications from preeclampsia are the main cause of newborn sickness and mortality in Ghana (Boafo et al., 2017).

2.2.4.3 Healthcare Burden:

Managing preeclampsia places a considerable burden on the healthcare system. It requires substantial resources for monitoring, hospitalization, and treatment.

Additionally, the need for emergency interventions, such as Caesarean sections, further strains healthcare facilities (Owiredu et al., 2012).

2.2.5 Sociocultural and Economic Factors

2.2.5.1 Access to Care:

In rural areas, inadequate access to high-quality antenatal care services worsens the effects of preeclampsia. Many women in remote regions may not receive timely diagnosis and management, leading to higher rates of complications (Ganle et al., 2019).

2.2.5.2 Awareness and Education:

There is a general lack of awareness and education about preeclampsia among pregnant women in Ghana. Increasing awareness of preeclampsia's signs and symptoms can facilitate its early detection and effective management (Omenyo, 2019).

2.2.5.3 Economic Impact:

The economic burden of preeclampsia is significant for affected families, particularly in low-income settings. The costs associated with treatment, transportation to healthcare facilities, and potential loss of income due to illness can be substantial (Bonsu et al., 2020).

Preeclampsia remains a significant public health issue in Ghana, significantly impacting maternal and neonatal health. Addressing the prevalence and impact of preeclampsia requires concerted efforts to improve access to antenatal care, raise awareness, and enhance healthcare infrastructure and resources.

2.2.6 Prevalence and Impact of Preeclampsia in Upper East Region

Preeclampsia is a significant health issue in Ghana's Upper East Region, contributing to maternal and neonatal morbidity and mortality.

2.2.6.1 Prevalence of Preeclampsia in Upper East Region:

Similar to other regions in Ghana, the Upper East Region experiences a substantial prevalence of preeclampsia. A study conducted at the Bolgatanga Regional Hospital reported a prevalence rate of approximately 7.2% among pregnant women (Azongo et al., 2019).

Many variables, including high rates of teenage pregnancies, limited access to high-quality prenatal care, and inadequate healthcare infrastructure, have been connected to the high frequency of preeclampsia in this region (Awuni, 2018).

2.2.7 The Impact of Preeclampsia in Upper East Region:

2.2.7.1 Maternal Health:

Preeclampsia significantly impacts maternal health, causing serious complications like eclampsia and HELLP syndrome. In the Upper East Region, it is a major factor in maternal health crises (Akilla et al., 2024; Azongo et al., 2019).

2.2.7.2 Perinatal Outcomes:

The condition also affects perinatal outcomes, leading to low birth weight, preterm birth, d intrauterine growth restriction (IUGR). Research indicates that preeclampsia-related complications are a leading cause of neonatal illness and fatalities in the region (Awuni, 2018).

2.2.7.3 Healthcare Burden:

Managing preeclampsia places a considerable burden on the healthcare system in the Upper East Region. The need for emergency interventions, such as Caesarean sections, and intensive neonatal care further strains healthcare resources (Akazili et al., 2011).

2.2.8 Sociocultural and Economic Factors:

2.2.8.1 Access to Care:

The limited availability of high-quality prenatal care in rural areas worsens the effects of preeclampsia. In these remote regions, many women may not get timely diagnoses and treatment, resulting in increased complication rates (Azongo et al., 2019).

2.2.8.2 Awareness and Education:

In the Upper East Region, there is a significant lack of awareness and education about preeclampsia among pregnant women. Enhancing the understanding and identification of its signs and symptoms can facilitate the early diagnosis and treatment of the condition (Awuni, 2018).

2.2.8.3 Economic Impact:

The economic burden of preeclampsia is significant for affected families, particularly in low-income settings. The costs associated with treatment, transportation to healthcare facilities, and potential loss of income due to illness can be substantial (Akazili et al., 2011).

Preeclampsia remains a significant issue of public health in the Upper East Region of Ghana, with significant impacts on the health of both mothers and newborns. Addressing the prevalence

and impact of preeclampsia requires concerted efforts to improve access to antenatal care, raise awareness, and enhance healthcare infrastructure and resources.

2.2.9 Prevalence of Preeclampsia Globally.

Preeclampsia is a significant global health issue affecting pregnant women and their babies, significantly contributing to illness and deaths in pregnancies. Its prevalence varies worldwide, with increased prevalence in lower-income regions, establishing it as one of the leading causes of pregnancy-related health issues. Worldwide, preeclampsia impacts approximately 2% to 8% of all pregnancies (Abalos et al., 2013).

The impact of preeclampsia extends beyond the immediate perinatal period, Women who have had it are more likely to suffer cardiovascular diseases such as hypertension and stroke in later life (Bellamy et al., 2007).

Furthermore, infants born to mothers with preeclampsia are at a greater risk of facing adverse birth outcomes such as preterm delivery, low birth weight, and long-term health problems (Adams et al., 2014; McDonald et al., 2008; von Dadelszen & Magee, 2008). Preeclampsia is a common pregnancy complication with varying prevalence rates globally. While it can affect women across all races and ethnicities, the risk factors and incidence rates differ among populations.

In wealthier nations, the prevalence is generally lower, ranging from 2% to 5% of pregnancies (Firoz et al., 2011; Goldenberg et al., 2011), largely due to enhanced availability of prenatal care, early diagnosis, and management. In contrast, preeclampsia is more prevalent in lower-income regions, where healthcare and prenatal services may be less accessible. In some areas, the prevalence can exceed 10% of pregnancies. Among these countries, prevalent rates are reported as; Zimbabwe (58%), China (38%), Cameroon (37.4%), Thailand (34%), Mauritius (34%), Réunion (31%), Guadeloupe (31%), Turkey (29%), and India (26%) (Firoz et al., 2011; Ratsiatosika et al., 2019). Several factors can elevate the risk of preeclampsia, such as being a

first-time mother or having a previous history of the condition, multiple gestations (e.g., twins or triplets), maternal age under 20 or over 40, and certain underlying health conditions like chronic hypertension or diabetes.

2.3 EARLY OBSERVATIONS AND NOMENCLATURE

Preeclampsia has a well-established history, with recorded descriptions originating from ancient civilizations. Early medical texts, including the Ebers Papyrus from ancient Egypt (Frey, 1986; Major, 1930; Von Klein, 1905) and the Hippocratic writings (Kibre, 1945), mention symptoms resembling those of preeclampsia. However, these descriptions were vague and often confused with other pregnancy-related conditions. This pregnancy-related condition has been recognized and documented for centuries, with its early observations and nomenclature offering a window into the historical understanding of this complex disorder. Historically, Preeclampsia's roots can be traced back to ancient times. In the past, it was often referred to by various names such as "toxaemia of pregnancy" or "pregnancy poisoning''(Cook & Lever, 1924; Dexter et al., 1943). Ancient medical texts and historical records contain descriptions of pregnant women experiencing symptoms consistent with preeclampsia (Chesley, 1984), though without the benefit of modern medical terminology or diagnostic tools. Before the term "preeclampsia" came into common use, the condition was primarily referred to as "eclampsia''(Ohme, 1934) . The term "eclampsia" originates from the Greek word meaning "a lightning strike" or "sudden appearance," capturing the sudden and unpredictable nature of the condition, (Hidaka & Nakamoto, 2014).

Eclampsia was characterized by seizures, which were a prominent feature of this condition. In the early 20th century, physicians began to identify key clinical features associated with preeclampsia (Baumwell & Karumanchi, 2007; Wagner, 2004). Two of the most significant observations were the presence of edema (swelling) and hypertension (high blood pressure) in

pregnant women. These hallmark signs marked the beginning of a more systematic understanding of the condition. Early days after the recognition of Preeclampsia as a pregnancy-related disease, pave way to the nomenclature describing the disease.

The term "preeclampsia" emerged as a way to differentiate the earlier stages of the condition from the more severe and life-threatening eclampsia (Baumwell & Karumanchi, 2007; Chesley, 1984; Wagner, 2004). "Pre-" means "before," indicating that preeclampsia occurs before the onset of labour. It encompasses a range of disorders marked by hypertension and seizures, as well as additional symptoms like proteinuria (protein in the urine) and organ dysfunction, (Sibai et al., 2003). Medical terminology has also evolved to address situations where preeclampsia complicates pre-existing hypertension. This condition, known as "superimposed preeclampsia," recognizes that Pregnant women who already have high blood pressure are more likely to experience preeclampsia (Guedes-Martins, 2017).

HELLP Syndrome, an advanced form of preeclampsia, is identified by Haemolysis, Elevated Liver Enzymes, and a Low Platelet count (Martin Jr et al., 1999). This syndrome is characterized by specific laboratory findings and clinical features. The name "HELLP" reflects these key characteristics and distinguishes it from other forms of preeclampsia. Over time, medical professionals have developed standardized diagnostic criteria to define and classify preeclampsia (August & Sibai, 2017; Conde-Agudelo et al., 2004). These criteria typically encompass hypertension, proteinuria, and occasionally other indicators of organ dysfunction, providing a more precise framework for diagnosis and management. The early observations and nomenclature of preeclampsia reflect the historical evolution of our understanding of this condition. The transition from "eclampsia" to "preeclampsia" marked a pivotal moment in recognizing the diverse clinical manifestations of this disorder and the need for standardized diagnostic terminology and criteria. Advances in medical science and ongoing research continue

to enhance our knowledge of preeclampsia, leading to improved care and outcomes for pregnant individuals.

2.4 PATHOPHYSIOLOGICAL THEORIES OF PREECLAMPSIA

Historically, various pathophysiological theories attempted to explain preeclampsia (Medjedovic et al., 2022; Rana et al., 2019). In the mid-20th century, researchers explored the role of renal dysfunction, vascular abnormalities, and immunological factors in its development. However, the exact cause remained unclear until recent research illuminated the complex interaction between maternal and placental factors. (Huppertz, 2015). Preeclampsia is a multifaceted and complex pregnancy condition marked by high blood pressure, proteinuria, and frequent organ dysfunction. Although the precise cause remains unknown, several pathophysiological theories have been proposed to explain the underlying mechanisms and contributing factors (Medjedovic et al., 2022). These theories provide valuable insights into our understanding of the condition. One prominent explanation is the Placental Insufficiency Theory (Huppertz, 2008; Mignini et al., 2005; Walker et al., 2015), which posits that preeclampsia primarily stems from insufficient blood flow and poor development of maternal-foetal circulation. When the placental blood vessels develop abnormally, it can result in decreased delivery of nutrients and oxygen to the foetus, leading to oxidative stress in the placenta (Schoots et al., 2018; Wu et al., 2015; Wu et al., 2016). This stress triggers the release of factors that result in vascular dysfunction and widespread inflammation in pregnancy (Wu et al., 2015). Ultimately, these changes lead to the clinical manifestations of the disease in pregnant women.

The immunological theory suggests that preeclampsia might be associated with an exaggerated maternal immune response to foetus antigens (Levron et al., 2014; Matthiesen et al., 2005; Schiessl, 2007). During pregnancy, the immune response of the pregnant individual must tolerate the semi-allogenic foetus (Levron et al., 2014). Disruption in this immune tolerance can lead to inflammation and endothelial damage, contributing to preeclampsia, (Boeldt & Bird, 2017; Kestlerova et al., 2012). Wide spread vascular dysfunction is a central feature of preeclampsia, (Boeldt & Bird, 2017; Gilbert et al., 2008). Abnormal placental perfusion and oxidative stress are believed to release vasoactive substances and proinflammatory cytokines (Gilbert et al., 2008; Poston, 2006). These substances disrupt with the normal function of maternal vascular structures, leading to vasoconstriction, increased vascular permeability, hypertension, and organ damage (Mutter & Karumanchi, 2008; Opichka et al., 2021).

When reactive oxygen species (ROS) outweighs antioxidants, oxidative stress occurs, playing a crucial role in the development of preeclampsia (Joo et al., 2021; Marín et al., 2020), causing cellular damage and endothelial dysfunction. This imbalance also results in the secretion of anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), which contribute to hypertension and other symptoms of preeclampsia (Wang et al., 2009).

There is also evidence suggesting that genetic factors might influence susceptibility to preeclampsia (Morgan & Ward, 1999). Some women may have genetic predispositions that make them more susceptible to the condition (Haram et al., 2014).

Variations in genes related to blood pressure regulation, endothelial function, and immune response have been investigated as potential contributors (Chen et al., 2014).

Vascular abnormalities, including impaired vascular remodeling and adaptation during pregnancy, are associated with preeclampsia (Boeldt & Bird, 2017; Opichka et al., 2021).

Insufficient adaptation of maternal blood vessels to the increased blood flow required by the placenta can result in vascular resistance, leading to hypertension and organ dysfunction (Hahad et al., 2019; Yart et al., 2021). Hormonal changes during pregnancy, which disrupt the renin-angiotensin system and cause fluctuations in placental hormone production (Leal et al., 2022; Shah, 2005), are also implicated in the onset of preeclampsia. Dysregulation of these hormonal pathways can increase blood pressure and lead to vascular dysfunction (Hahad et al., 2019; Yart et al., 2021). Preeclampsia is a complex, multifactorial condition, and the various pathophysiological theories likely interact and contribute to its development to different extents in different individuals. Ongoing research is essential to further understand these underlying mechanisms, which will help improve diagnostic and therapeutic strategies to manage this gestational disease and reduce its impact on the foetal and maternal and health.

It is important to acknowledge that preeclampsia is a multifaceted condition with several contributing factors, and the various pathophysiological theories are likely interrelated. These theories interact and play different roles in the occurrence of preeclampsia among pregnant individuals. Continued research is essential to deepen our understanding of the underlying mechanisms of this condition, which will aid in developing improved diagnostic and therapeutic strategies to manage preeclampsia and mitigate its effects on the foetus and maternal health.

2.5 PATHOPHYSIOLOGICAL MECHANISM AND CLINICAL FEATURES

Preeclampsia is primarily considered a placental disorder. Abnormal placentation, marked by insufficient trophoblast infiltration and inadequate modification of spiral arteries, results in diminished blood flow to the placenta, thus placental dysfunction (Walker et al., 2015). This, in turn, triggers a cascade of events as shown in Figure 1.

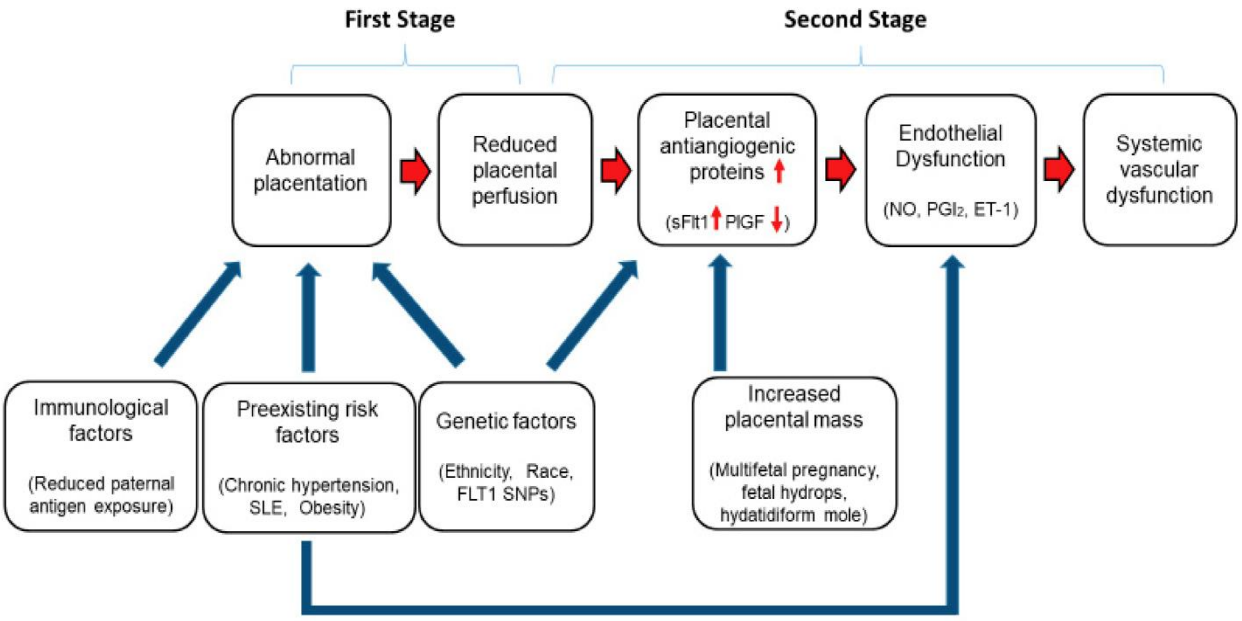

Figure 1: *Two-stage theory of the pathophysiology of preeclampsia*

(IJMS | Free Full-Text | Preeclampsia: Maternal Systemic Vascular Disorder)(Tomimatsu et al., 2019)

Among the key events that ensue include, reduced blood flow to organs, including the maternal endothelium, which leads to disseminated vascular dysfunction, as a central feature of preeclampsia (Boeldt & Bird, 2017; Gilbert et al., 2008). The damaged endothelium loses its vasodilatory and anti-thrombotic properties and becomes pro-inflammatory and pro-coagulant. The imbalance between vasoconstriction and vasodilation, often due to endothelial dysfunction, leads to increased peripheral vascular resistance, causing hypertension a hallmark of preeclampsia. Vascular dysfunction plays a crucial role in the onset of preeclampsia and is frequently associated with a systemic inflammatory response, marked by the release of pro-inflammatory cytokines and chemokines (Raghupathy, 2013; Visser et al., 2007). This inflammatory environment further harms endothelial cells and contributes to multi-organ dysfunction, affecting the liver, kidneys, and even the blood. The persistent hypoxia-reoxygenation environment in preeclampsia increases levels of reactive oxygen species (ROS) and can result in uteroplacental insufficiency, increasing cell death. Preeclampsia causes an

imbalance between reactive oxygen species (ROS) and antioxidants, leading to oxidative stress (Taravati & Tohidi, 2018), which damages cells and tissues and worsens the inflammatory response.

The placenta is crucial in the development of preeclampsia. Insufficient blood flow to the placenta and abnormal uteroplacental circulation can lead to placental ischaemia and hypoxia, resulting in placental dysfunction (Boeldt & Bird, 2017; Gilbert et al., 2008; Zárate et al., 2014). In response, the placenta releases various bioactive molecules into the maternal bloodstream, including anti-angiogenic factors like soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), which disrupt blood vessel development and function, (Ali et al., 2019; Dahabiyeh, 2018). These factors, along with oxidative stress and inflammation, damage the maternal endothelium (Boeldt & Bird, 2017; Gilbert et al., 2008), leading to constriction of blood vessels, increased vascular permeability, and a heightened inflammatory response. This state of systemic inflammation is driven by proinflammatory Cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which plays a role in endothelial dysfunction (Sprague & Khalil, 2009; Xie et al., 2011). The damaged endothelium fails to regulate blood pressure properly, leading to hypertension, which in turn activates the renin-angiotensin-aldosterone system and further exacerbates the condition (Leal et al., 2022). This persistent increase in blood pressure, coupled with liver and kidney dysfunction, can result in pulmonary edema, a possible complication of preeclampsia (August & Sibai, 2017; Lambert et al., 2014; Norwitz et al., 2002).

In severe cases, there can be coagulation abnormalities and central nervous system involvement. In preeclampsia, there is frequently an imbalance in angiogenic factors like vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) (Ali et al., 2019; Dahabiyeh, 2018). Endothelial dysfunction is associated with decreased PlGF levels and increased sFlt-1 levels

(Gurnadi et al., 2015). The underlying mechanisms of preeclampsia, a condition that affects almost every organ, also involve increased activation of the blood clotting system (Ives et al., 2020; Kenny et al., 2009; ZEEMAN & DEKKER, 1992), raising the risk of thrombotic events.

2.6 AETIOLOGICAL RISK FACTORS FOR PREECLAMPSIA

Preeclampsia is a multifaceted condition marked by hypertension, proteinuria, and involvement of multiple organs, predominantly affecting pregnant women. Recognizing its risk factors and underlying causes is vital for early detection, prevention, and effective management.

Below are some of the risk factors illustrated in the Figure 2:

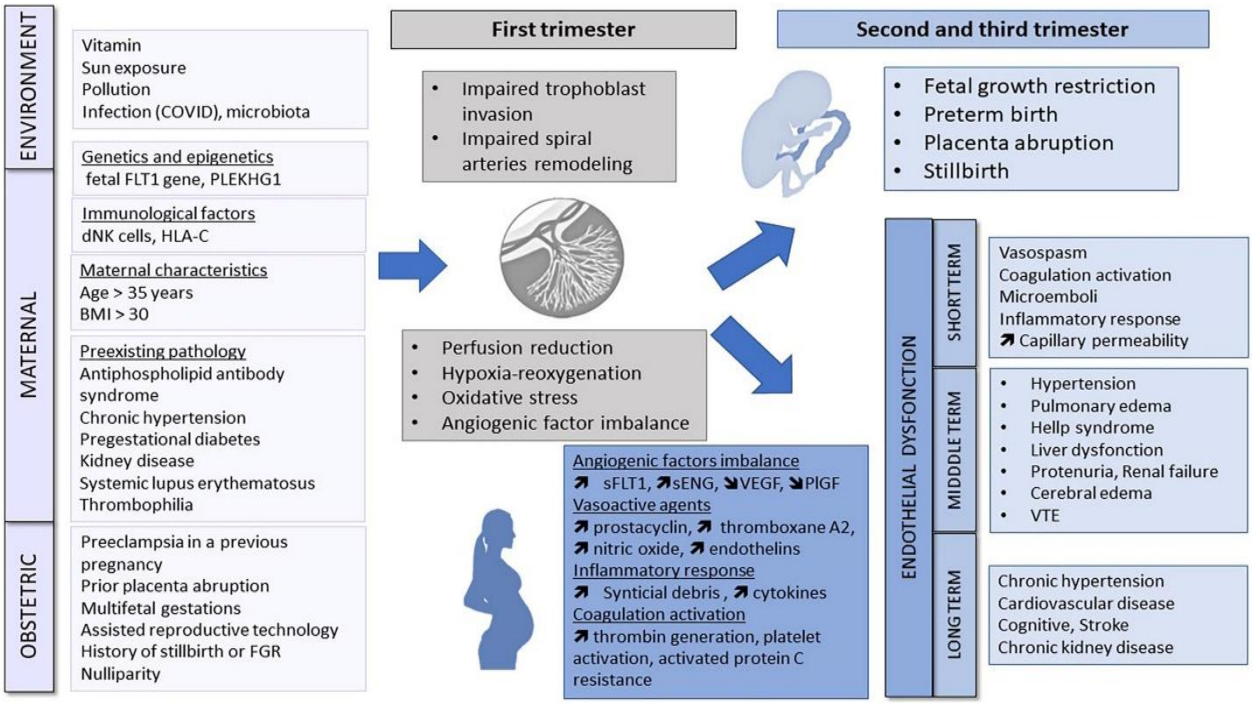

Figure 2: *Pathogenesis of pre-eclampsia (Frontiers in cardiovascular medicine, 9, 856923*.**)** (Raia-Barjat et al., 2022).

Preeclampsia is a complex pregnancy condition that is impacted by maternal, foetus, genetic, immunological, and vascular factors. Understanding its risk factors and causes is vital for early detection, risk assessment, and developing targeted preventive and therapeutic strategies to

improve maternal and foetus outcomes. Ongoing research continues to refine our understanding of the complex mechanisms behind this condition's risk factors, such as:

2.6.1 Maternal age:

Preeclampsia is known to be associated with advanced maternal age, which is often interpreted as 35 years of age or older (Walker & Thornton, 2016). The altered vascular function associated with ageing is probably the cause of the higher risk in older pregnant women

2.6.2 First pregnancy:

Preeclampsia is linked to primiparity, or being pregnant for the first time (Luo et al., 2007). While the exact reasons for this association are not fully understood, it may relate to the maternal immune system's response to paternal antigens. The relationship between this link and the mother's immune system's reaction to paternal antigens is unclear, but it could have something to do with it.

2.6.3 Previous history of preeclampsia:

Preeclampsia is more likely to develop in subsequent pregnancies in women who have previously had it (Carty et al., 2010), indicating that maternal factors are likely to be important.

2.6.4Multiple gestations:

Pregnancies involving twins or triplets face a greater risk of preeclampsia because of the increased placental mass and higher demands on maternal circulation (Bdolah et al., 2008).

2.6.5Obesity:

One of the main risk factors for preeclampsia is maternal obesity, which is characterized by a high body mass index (BMI) (El-Makhzangy et al., 2010; Poorolajal & Jenabi, 2016). Endothelial dysfunction and chronic inflammation are linked to obesity.

2.6.6 Chronic Hypertension:

Preeclampsia during pregnancy is more common in women who already have hypertension (Catov et al., 2007), suggesting that underlying vascular variables have a role in the development of the illness.

2.6.7 Diabetes:

Gestational diabetes and pre-existing diabetes (type 1 or type 2) increase the risk of preeclampsia (Catov et al., 2007). This is probably because they have an effect on inflammation and vascular function.

2.6.8 Autoimmune disorders:

Preeclampsia is linked to an increased incidence of conditions including antiphospholipid syndrome and systemic lupus erythematosus (SLE) (Fischer-Betz & Specker, 2017), possibly as a result of immune system imbalance.

2.6.9 Family history:

A woman's risk may be increased if there is a family history of preeclampsia (Fischer-Betz & Specker, 2017), indicating a possible genetic predisposition to the illness.

2.6.10 Placental Factors:

Preeclampsia partially arises from issues related to the placenta. The condition may be triggered by abnormalities in placental development and function, such as inadequate placental perfusion and improper remodeling of spiral arteries (Huppertz, 2008; Mignini et al., 2005; Walker et al., 2015).

2.6.11 Immunological factors:

An alteration in the maternal immune system's reaction to the foetus and placenta (Levron et al., 2014; Matthiesen et al., 2005; Schiessl, 2007), often related to abnormal trophoblast invasion, is thought to contribute to preeclampsia.

2.6.12 Vascular factors:

Endothelial dysfunction and impaired maternal vascular adaptation to pregnancy are key aspects of preeclampsia pathophysiology (Boeldt & Bird, 2017; Opichka et al., 2021), leading to hypertension and multi-organ damage.

2.6.13 Genetic factors:

There is evidence to suggest a genetic predisposition to preeclampsia (Haram et al., 2014). Certain genetic variations in both maternal, and foetus genes may increase susceptibility.

2.6.14 Inflammation:

Chronic inflammation is associated with preeclampsia (Harmon et al., 2016), with elevated quantities of inflammatory markers contributing to endothelial dysfunction and organ damage.

2.6.15 Oxidative Stress:

Elevated oxidative stress, caused by an imbalance between free radicals and antioxidants, is thought to contribute to the development of preeclampsia (Al-Gubory et al., 2010; Negi et al., 2011; Taravati & Tohidi, 2018; Taysi et al., 2019).

2.7 CONTEMPORARY UNDERSTANDING AND RESEARCH

Over the past few years, our comprehension of preeclampsia has evolved significantly. It is now recognized as a complex, multi-system disorder with contributions from both maternal and placental factors (Abbas et al., 2021). Research has identified biomarkers including angiogenic factors, which are involved in its development, (Herraiz et al., 2015; Stepan et al., 2020). Additionally, the genetic and epigenetic aspects of preeclampsia (Haram et al., 2014), are areas of active investigation. In recent years, our contemporary understanding of preeclampsia has advanced significantly, shedding light on its complex pathophysiology, risk factors, diagnosis, and potential management strategies. As the precise aetiology of preeclampsia is still unknown, there is a growing understanding of how placental insufficiency contributes to its complex and

multifactorial pathogenesis. The disease is exacerbated by oxidative stress, inflammation, and immunological dysfunction. An imbalance situation at the placenta level that exists between proangiogenic factors (VEGF) and antiangiogenic factors (soluble fms-like tyrosine kinase-1, or sFlt-1) (Ali et al., 2019). This situation is increasingly recognized as a critical element in causing endothelial dysfunction and hypertension. Additionally, genetic research has pinpointed specific susceptibility genes and polymorphisms that may increase the likelihood of developing preeclampsia in some individuals. Advances in genetics and epigenetics have revealed potential genetic and epigenetic contributions to preeclampsia (Apicella et al., 2019; Kamrani et al., 2019). Changes in epigenetic, such as DNA methylation and the involvement of microRNAs, are also being explored for their potential roles in preeclampsia, (Apicella et al., 2019; Kamrani et al., 2019). Recent review of the literature have revealed remarkably, the gains made by researchers, who are actively exploring biomarkers to improve early detection, and risk assessment for preeclampsia (Dahabiyeh, 2018). Potential biomarkers under investigation include placental growth factor (PlGF) and the sFlt-1/PlGF ratio (Ali et al., 2019), and other proteins and metabolites associated with endothelial dysfunction and inflammation (Dahabiyeh, 2018). These biomarkers hold the potential for more accurate and timely diagnosis. Contemporary research aims to develop risk prediction models (De Kat et al., 2019; Thangaratinam et al., 2017; Wright et al., 2019), to determine which females are more susceptible to preeclampsia. By assessing various clinical, demographic, and biomarker factors, researchers are working toward more personalized risk assessment. Furthermore, preventive strategies, including the use of low-dose aspirin, are being explored to reduce the risk of preeclampsia in high-risk individuals. Recent studies have also focused on enhancing the management of preeclampsia, especially in cases that are severe or have an early onset, (Le et al., 2019). Advances in guidelines have refined recommendations for delivery timing, blood pressure control, and the use of magnesium sulfate to prevent seizures, (Roberts et al., 2002).

New treatment strategies, such as administering antenatal corticosteroids to aid foetus lung development, are being investigated. Modern research acknowledges the potential long-term health impacts of preeclampsia on both mothers and their children. Studies are examining the elevated risk of cardiovascular disease, metabolic disorders, and other health issues in women who have experienced preeclampsia, as well as the health outcomes for children exposed to preeclampsia in the womb (Andraweera et al., 2020; Lu & Hu, 2019; Sacks et al., 2018). Most recent researchers are seeking novel approaches to addressing the disparities in the burden of preeclampsia and working on strategies to improve access to prenatal care, early identification and management in settings with limited resources (Atluri et al., 2023; Dippenaar et al., 2022; Vasco et al., 2019), as a major worldwide health concern, especially in low income nations. There is ongoing research which is focusing on the importance of patient-centered care in managing preeclampsia (Geissler et al., 2023; Seely et al., 2021; Tsigas, 2022). Informed consent, shared decision-making, and psychological support for women affected by preeclampsia. Contemporary understanding and research on preeclampsia have made significant strides in unraveling the complex nature of this condition. Researchers are exploring new diagnostic tools, preventive measures, and treatment strategies aimed at enhancing outcomes for both mothers and their infants. As ongoing research advances our knowledge, healthcare providers can provide more effective care and support to pregnant individuals at risk of preeclampsia.

2.8 Advances in Diagnostic Criteria of Preeclampsia

The early 20th century witnessed significant advancements in recognizing and diagnosing preeclampsia. Researchers such as John Whitridge Williams (Eastman, 1964) and Chesley introduced more systematic diagnostic criteria, emphasizing the triad of hypertension, proteinuria, and edema (Chesley, 1985). These criteria provided a standardized framework for

identifying and classifying preeclampsia cases. A pregnancy-related condition; preeclampsia is characterized by elevated blood pressure and impairment to several organ systems. Over the years, advances in medical knowledge and technology have led to refinements in the diagnostic criteria for preeclampsia (Bell, 2010). In recent times, we have witnessed advances, geared toward the improvement in diagnostic criteria, subsequently improving our understanding of the condition and enhancing the ability of individuals who are at risk of the disease. Early and precise diagnosis is essential for effectively managing preeclampsia and reducing associated complications for both mother and baby. Traditionally, preeclampsia was identified when a pregnant person's blood pressure was at least 140/90 mm Hg. However, recent developments have refined these criteria. The American College of Obstetricians and Gynaecologists (ACOG) now emphasizes the importance of having a baseline blood pressure measurement before pregnancy for accurate diagnosis (Hurrell et al., 2022), as blood pressure may vary among individuals. Additionally, the ACOG recommends considering different thresholds for individuals with preexisting hypertension, as well as lower thresholds for women with gestational hypertension. Previously, proteinuria was a key diagnostic criterion for preeclampsia. However, experts have realized that preeclampsia can occur without significant proteinuria (Dong et al., 2017; Özkara et al., 2018). As a result, diagnosis can also be based on other indicators of organ dysfunction, such as liver impairment, reduced platelet count, or kidney issues. New diagnostic criteria emphasize the importance of the inclusion of these organ dysfunctions (Bartal et al., 2022; Sani et al., 2019), as additional identifiable characteristic which will optimize the disease diagnosis, even in the absence of substantial proteinuria. Recognizing the limitations of relying on a single diagnostic parameter, modern approaches to preeclampsia diagnosis incorporate a combination of clinical and laboratory assessments (Duhig et al., 2018; Peck Palmer & Das, 2020). These may include blood pressure measurements, proteinuria, liver function tests, and platelet counts. The integration of multiple markers allows

for a more comprehensive evaluation of the individual's condition and helps healthcare providers make a more accurate diagnosis. Diagnostic criteria for a severe variant of preeclampsia, HELLP syndrome have been refined to include specific laboratory findings (Lisonkova et al., 2020).

Research into novel biomarkers associated with preeclampsia has led to advancements in diagnostic criteria (Lim et al., 2021). Biomarkers such as soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) have demonstrated potential in early preeclampsia detection, (Herraiz et al., 2015; Stepan et al., 2020). The sFlt-1/PlGF ratio has been particularly effective in identifying individuals at high risk for preeclampsia in women (Aminuddin et al., 2022). Advances in technology have led to the development of various risk prediction models designed to assess the likelihood of preeclampsia, (De Kat et al., 2019; Thangaratinam et al., 2017; Wright et al., 2019). These models consider various factors such as medical history, maternal characteristics, and biomarker levels. The use of risk prediction models allows for a personalized approach to monitoring and managing pregnant individuals at different risk levels.

Recent progress in imaging methods, including Doppler ultrasound, has been utilized to assess blood flow within the uterine arteries, (Sciscione & Hayes, 2009). Abnormal blood flow through the uterine arteries is a potential risk factor for the pathogenesis of preeclampsia (Anastasakis et al., 2008; Sciscione & Hayes, 2009), and these findings can aid in early diagnosis and risk stratification.

These advances in diagnostic criteria for preeclampsia have greatly improved the ability to identify and manage the condition. Early diagnosis and risk assessment allow for timely interventions, close monitoring, and personalized care, ultimately reducing the risk of complications for both the pregnant individual and the developing foetus. Healthcare providers need to stay up-to-date with these evolving diagnostic criteria to ensure the best possible outcomes for pregnant individuals at risk of preeclampsia.

2.9 CLINICAL FEATURES OF PREECLAMPSIA:

After 20 weeks of pregnancy, high blood pressure is the hallmark of a rare and complex pregnancy-related disease called preeclampsia, which is frequently accompanied by proteinuria or other indicators of end-organ failure (Chalas, 2020; Chen et al., 2023; Malha et al., 2024; Rebarber, 2019). Preeclampsia's clinical signs and symptoms include:

2.9.1 Hypertension:

A hallmark of preeclampsia is elevated blood pressure, which is defined as a systolic reading of 140 mm Hg or more, or a diastolic reading of 90 mm Hg or more, measured on two separate occasions after 20 weeks of pregnancy, with at least 4 hours between measurements.

2.9.2Proteinuria:

which denotes an abnormal amount of protein in the urine. This is usually defined as 300 mg or more of protein in a 24-hour urine sample or a urine protein-to-creatinine ratio of 0.3 or greater.

2.9.3 Edema:

Although swelling (edema) is frequently associated with preeclampsia, it is not used as a diagnostic criterion. When it does occur, edema is usually generalized rather than confined to the hands or face.

2.9.4 Multi-Organ Involvement:

Preeclampsia can impact various organ systems, manifesting as headaches, visual disturbances, epigastric pain, liver and kidney dysfunction, and pulmonary edema. In severe cases, it can lead to seizures, a condition referred to as eclampsia.

2.9.5 Foetus growth restriction:

Preeclampsia can cause insufficient blood flow to the placenta, which may result in foetus growth restriction and an increased risk of preterm birth.

2.9.6 Headaches:

Severe headaches that don't go away with over-the-counter painkillers could be a sign of preeclampsia.

2.9.7 Visual disturbances:

Vision changes, including blurriness, light flashes, or visual disturbances, are alarming indicators of preeclampsia.

2.9.8 Right Upper Quadrant Pain or Epigastric:

Intense pain in the upper abdomen, just beneath the ribs, can signify liver involvement in preeclampsia.

2.9.9 Seizures:

In severe instances, preeclampsia can advance to eclampsia, characterized by the occurrence of seizures.

***2.9.10 Decreased foetus movements*:**

Preeclampsia can reduce blood flow to the placenta, impacting foetus well-being. Reduced foetus movements may indicate distress. Preeclampsia is a complex and dynamic condition with diverse clinical presentations. Early detection, careful monitoring, and timely intervention are crucial to prevent and manage this potentially life-threatening condition, safeguarding the health of both mother and baby.

2.10 DEFINITION CRITERIA FOR PREECLAMPSIA

High blood pressure that appears after the 20th week of pregnancy and is linked to proteinuria or other indications of organ malfunction is known as preeclampsia (Chalas, 2020; Chen et al., 2023; Malha et al., 2024; Rebarber, 2019) :

2.10.1 Hypertension:

A woman previously normotensive before 20 weeks of gestation is diagnosed with preeclampsia if she records a systolic blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher, on two separate occasions at least 4 hours apart.

2.10.2 Proteinuria:

When a 24-hour urine sample has 300 milligrams or more of protein excreted, or when the protein-to-creatinine ratio is 0.3 or higher, proteinuria is identified.

2.10.3 End-Organ Dysfunction:

If there is evidence of end-organ malfunction, preeclampsia can still be diagnosed in the absence of proteinuria. These include thrombocytopenia (platelet count < 100,000/microliter), elevated liver enzymes, pulmonary oedema, new-onset renal insufficiency (> 1.1 mg/dL or doubling of serum creatinine without underlying renal disease) (Chen et al., 2023), and cerebral or visual symptoms.

2.11 MANAGEMENT OF PREECLAMPSIA

Preeclampsia is a serious pregnancy-related condition that needs to be carefully managed by clinicians and medical professionals to safeguard the health of the mother and the developing foetus. An early diagnosis, close observation, and appropriate measures to lower risks and avoid problems are all parts of proper care.

2.11.1 Clinical management of preeclampsia:

2.11.1.1 Close monitoring:

Pregnant individuals diagnosed with preeclampsia should be closely monitored by healthcare providers. Monitoring includes regular blood pressure measurements, assessment of organ function (including liver and kidney function), and foetus surveillance through methods like ultrasound and non-stress tests.

2.11.1.2 Hospitalization:

Hospitalisation may be necessary, depending on the severity of preeclampsia and the gestational age of the foetus. Hospitalization allows for close monitoring and the prompt initiation of treatment, especially in cases of severe preeclampsia.

2.11.1.3 Medications:

The severity of preeclampsia and the foetus's gestational age influence the selection and timing of drugs. Medications that may be used include:

2.11.1.4 Antihypertensives:

Used to control high blood pressure and minimize the risk of complications.

2.11.1.5 Magnesium Sulfate:

Given to patients with severe preeclampsia and eclampsia to stop seizures.

2.11.1.6 Corticosteroids:

To accelerate foetus lung maturation in cases of preterm preeclampsia.

2.11.1.7 Antiplatelet Agents:

Low-dose aspirin may be recommended for certain high-risk individuals to prevent preeclampsia.

2.11.1.8 Delivery:

The delivery of the baby is the only treatment that can truly cure preeclampsia. The foetus's gestational age, the severity of the mother's condition, and the general health of the mother and child all influence when the baby should be delivered. Even though the foetus is not yet full-term, in some circumstances it can be necessary to proceed with an early delivery in order to avoid serious complications.

2.11.1.9 Postpartum Monitoring:

Preeclampsia can persist or even develop postpartum. Mothers who have preeclampsia require continued monitoring of their blood pressure and overall health during the postpartum period.

2.11.1.10 Long-Term Follow-Up:

Given the potential long-term health consequences of preeclampsia, individuals who have had preeclampsia should have long-term follow-up care to monitor their cardiovascular health. Preeclampsia is a dynamic and multifaceted condition, and its management must be tailored to the specific circumstances of each case. Early detection, specialized medical care, and collaborative decision-making with healthcare providers are essential for achieving the best outcomes for both the infant and mother.

2.11.2 Medical management of preeclampsia:

2.11.2.1 Blood pressure control:

One of the top priorities is to control hypertension. To lower blood pressure and lessen the chance of problems, doctors may prescribe antihypertensive drugs such as methyldopa, labetalol, or nifedipine.

2.11.2.2 Seizure prophylaxis:

Women with severe preeclampsia or those at high risk of developing eclampsia are often given magnesium sulphate to avoid seizures.

2.11.2.3 Corticosteroids:

In cases of severe preeclampsia or when preterm birth is anticipated, corticosteroids may be given to accelerate foetus lung maturation.

2.11.2.4 Delivery planning:

Delivering the baby and placenta is the final treatment for preeclampsia. The severity of the ailment, the gestational age, and the health of the mother and foetus all influence when and how the baby is delivered. For mild preeclampsia near term, induction of labour or a planned Caesarean section may be advised. In severe cases of preeclampsia, even when the foetus has not attained full maturity, an early delivery may be required to safeguard the mother's and the foetus's health.

2.11.2.5 Monitoring:

Women with preeclampsia require close monitoring, which may include daily blood pressure checks, regular urine protein assessments, and foetus surveillance.

2.11.2.6 Hospitalization:

In severe cases, hospitalization is often necessary to closely monitor maternal and foetus well-being, administer medications, and manage potential complications.

2.11.2.7 Postpartum Care:

Preeclampsia can persist or develop after delivery. Women with preeclampsia should continue to be monitored postpartum for any signs of worsening hypertension or other complications.

2.11.2.8 Follow-Up:

Women who have experienced preeclampsia should be closely monitored going forward since they may be more susceptible to cardiovascular disease and other conditions. Effective management of preeclampsia requires a collaborative approach involving obstetricians, nurses, neonatologists, and other healthcare specialists to ensure optimal outcomes for both baby and mother. Early detection, careful monitoring, and timely intervention are crucial for reducing the risks associated with this condition.

2.11.3 Imaging Studies in Preeclampsia Management:

Ultrasound:

Ultrasound is a valuable imaging tool during pregnancy and may be used in preeclampsia for various purposes:

2.11.3.1Foetus Assessment:

Ultrasound can help monitor foetus growth and development. It can assess factors such as foetus size, amniotic fluid volume, and foetus well-being.

2.11.3.2 Umbilical Artery Doppler:

This is a specialized ultrasound technique that assesses blood flow in the umbilical artery. Abnormal Doppler waveforms can be an indicator of placental insufficiency and may necessitate closer monitoring or early delivery.

2.11.3.3 Cervical Length Measurement:

In cases where preeclampsia necessitates early delivery, measuring cervical length via ultrasound can help determine the readiness for induction of labour or Caesarean section.

2.11.3.4 Non-Stress Test (NST):

The non-stress test (NST) is a straightforward, non-invasive procedure used to track the foetus heart rate in response to the baby's movements. It may be used as a means of assessing foetus well-being in the context of preeclampsia.

2.11.3.5 Biophysical Profile (BPP):

BPP combines ultrasound assessment of foetus well-being with NST. It assesses foetus breathing movements, large body movements, muscle tone, the volume of amniotic fluid, and the results from the non-stress test (NST) to offer a more thorough evaluation of the foetus.

2.11.3.6 Magnetic Resonance Imaging (MRI):

MRI is not typically used for routine imaging in preeclampsia but may be considered in particular circumstances. It is typically reserved for cases where there are atypical symptoms or complications such as severe neurological symptoms. MRI can help assess the extent of cerebral edema, haemorrhage, or other brain abnormalities.

2.11.3.7 Computed Tomography (CT):

Similar to MRI, CT scans are not commonly used in the evaluation of preeclampsia. They may be considered in rare cases with severe neurological symptoms to assess brain abnormalities.

It's crucial to stress that, although these imaging tests may be helpful in some circumstances, clinical evaluations are ultimately what determine preeclampsia diagnosis and therapy.

and laboratory findings, such as blood pressure measurements, urine protein analysis, and blood tests. Imaging studies, when employed, are intended to provide complementary information to support clinical decision-making. However, healthcare providers use Imaging studies for assessments to determine the severity of the condition, the need for intervention, and the timing of delivery.

2.12 MATERNAL AND FOETUS OUTCOMES

In the past, preeclampsia was linked to high rates of maternal mortality, (Ghulmiyyah & Sibai, 2012). Before the advent of modern medical interventions, Severe cases frequently progressed to eclampsia, a potentially fatal illness characterized by convulsions (Hidaka & Nakamoto, 2014). Improved diagnostic and management strategies, including antihypertensive medications, helped reduce maternal mortality. Foetus outcomes in preeclampsia have also been a focus of historical research. Preterm births and stillbirths were shown to be more common in preeclamptic pregnancies, according to early observations (Harmon et al., 2015; Smith et al., 2007). Preterm infants born to women with preeclampsia now have far higher survival rates thanks to advancements in neonatal care.

Preeclampsia is a serious pregnancy-related condition with potentially significant effects on both maternal and foetus outcomes. The severity of the condition can vary widely, and early detection and appropriate management are crucial in improving outcomes (Duhig et al., 2018).

Preeclampsia is marked by elevated blood pressure, which can pose risks to the mother. Severe hypertension can lead to complications such as stroke, organ damage (e.g., kidney, liver), and cardiovascular issues (August & Sibai, 2017; Norwitz et al., 2002).

Additionally, the disease can affect multiple organ systems, leading to problems like liver dysfunction, kidney dysfunction, and pulmonary edema (August & Sibai, 2017; Lambert et al., 2014; Norwitz et al., 2002). In severe cases, these complications can be life-threatening.

Furthermore, Some women with preeclampsia develop HELLP syndrome (Lisonkova et al., 2020). This severe form of preeclampsia poses significant risks to the mother. Without appropriate management, it can escalate to eclampsia, which is characterized by seizures, (Hidaka & Nakamoto, 2014). Eclampsia is a serious condition that can result in significant complications for both the mother and the foetus. Women who have experienced preeclampsia are also at a higher risk of developing long-term cardiovascular issues later in life, including hypertension, heart disease, and stroke (Lee & Tubby, 2015). Moreover, preeclampsia increases the risk of placental abruption, where the placenta detaches prematurely from the uterine wall, potentially causing severe bleeding and threatening the health of both the mother and baby (Lindqvist & Happach, 2006), potentially causing severe bleeding and jeopardizing the health of both mother and baby. The foetus may also face various complications, such as Intrauterine Growth Restriction (IUGR) due to reduced placental blood flow, which decreases the oxygen and nutrient supply and impairs foetus growth (Marseglia et al., 2016), where the baby does not grow at the expected rate.

Preeclampsia is also associated with Preterm Birth (Davies et al., 2016), where healthcare providers may recommend early delivery of the baby, thus Preterm birth. Preterm birth can result in several complications, such as respiratory distress syndrome and developmental problems (Mahoney & Jain, 2013), these birth outcomes often necessitate neonatal intensive care unit (NICU) support due to prematurity or other health concerns. Infants born to mothers with preeclampsia face a higher risk of low birth weight (LBW) (Ødegård et al., 2000), foetus distress, and stillbirth (Harmon et al., 2015); which can be profoundly distressing for the mother and her family. Research (Andraweera et al., 2020; Bokslag et al., 2016; Lu & Hu, 2019; Sacks et al., 2018; Wu et al., 2009) indicates that babies exposed to preeclampsia in utero may face an increased risk of long-term health issues, including cardiovascular and metabolic disorders, extending into childhood and adulthood.

2.13 General Overview of Sociodemographic, obstetric, and Clinical Characteristics of Preeclamptic Women.

Understanding the sociodemographic and clinical profiles of women with preeclampsia is essential for evaluating risk, ensuring early detection, and tailoring individualized treatment. Examining the demographic, obstetric, and clinical factors linked to preeclampsia is highly important for effective management and intervention.

2.14 Sociodemographic, Obstetric, and clinical characteristics Risk Factors for preeclampsia

Preeclampsia is a multifaceted condition defined by specific diagnostic criteria, which poses a major global challenge to maternal and neonatal health. It is associated with various sociodemographic and obstetric risk factors. Recognizing these risk factors and diagnostic criteria is crucial for early detection and for taking preventive actions to mitigate the negative outcomes of this serious pregnancy disorder. Numerous sociodemographic and Obstetric factors have been identified as possible risk factors for preeclampsia, including:

2.14.1 Sociodemographic Risk Factors

2.14.1.1 Maternal Age:

Both very young maternal age (under 18 years) and older maternal age (over 35 years) are linked to a higher risk of preeclampsia (Walker & Thornton, 2016).

2.14.1.2 Race and Ethnicity:

Preeclampsia has been observed to occur more frequently in certain racial and ethnic groups (Johnson & Louis, 2022). The incidence varies among racial and ethnic groups. Black women have a higher risk compared to white women, and other minority groups also encounter increased risks (Knuist et al., 1998).

2.14.1.3 Family History:

A family history of preeclampsia, especially if a mother or sister has had the condition, can raise an individual's risk of developing it (Fischer-Betz & Specker, 2017). Genetic factors may contribute to this increased risk.

2.14.1.4 Medical History:

Preeclampsia risk can be increased by several pre-existing medical diseases, such as diabetes, kidney illness, autoimmune disorders, and persistent hypertension (Carty et al., 2010).

2.14.1.5 Body Mass Index (BMI):

Preeclampsia is known to be associated with obesity, which is defined as a BMI of 30 or more (El-Makhzangy et al., 2010; Poorolajal & Jenabi, 2016). Increased insulin resistance and inflammation are linked to being overweight or obese, and these factors may hasten the onset of preeclampsia.

2.14.1.6 Socioeconomic Status:

Lower socioeconomic status and limited access to healthcare are associated with an increased risk of developing preeclampsia (Haelterman et al., 2003; Silva et al., 2008). Inadequate prenatal care and poor nutrition often associated with lower socioeconomic conditions may increase this risk.

2.14.2 Obstetric risk factors for Preeclampsia:

2.14.2.1 First Pregnancy:

Primigravidae, or first-time mothers, are more likely to develop preeclampsia than are women who have given birth before (Luo et al., 2007).

2.14.2.2 Multiple Gestations:

Multiple foetuses, such as twins or triplets, increase the risk of preeclampsia because of the added strain on the placenta and higher volume of blood (Haelterman et al., 2003).

2.14.2.3 The interval between Pregnancies:

Short intervals between pregnancies, specifically less than 18 months, could raise the likelihood of developing preeclampsia, (Shamsi et al., 2013).

2.14.2.4 Previous Preeclampsia:

A previous history of preeclampsia raises the likelihood of experiencing it again in future pregnancies, (Carty et al., 2010; Shamsi et al., 2013).

2.14.2.5 Molar Pregnancy:

Individuals who are pregnant with molars, a rare kind of anomalous pregnancy, (Mehta & Young, 1987).

2.14.2.6 Hydatidiform Mole:

A history of hydatidiform mole, a rare pregnancy complication, is linked to a higher chance of developing preeclampsia (Mehta & Young, 1987).

2.14.2.7 Chronic Hypertension:

Having hypertension before becoming pregnant increases the chance of preeclampsia (Catov et al., 2007).

2.14.2.8 Diabetes:

Preeclampsia is more likely to occur when diabetes is present, regardless of type

(Catov et al., 2007).

2.14.2.9 kidney disease:

Presence of renal disease increases the risk of preeclampsia in women (Wiles et al., 2018).

2.14.2.10 Autoimmune Diseases:

Preeclampsia is more common in patients with diseases such as antiphospholipid syndrome and systemic lupus erythematosus (Fischer-Betz & Specker, 2017).

2.14.3 Clinical characteristics in preeclampsia.

2.14.3.1 Blood Pressure:

Preeclampsia is marked by elevated blood pressure, defined as measurements of 140/90 mm Hg or higher, which is a key indicator of this condition.

2.14.3.2 Proteinuria:

Another sign that distinguishes preeclampsia is the presence of excessive protein in the urine or proteinuria. This can be determined by measuring the protein-to-creatinine ratio or by collecting urine for a full day.

2.14.3.3 Gestational Age:

Preeclampsia typically develops after 20 weeks of gestation but may develop at any stage during the latter half of pregnancy or even in the first few weeks after giving birth.

2.14.3.4 Obesity:

Preeclampsia is significantly increased by maternal obesity, which is frequently indicated by an elevated body mass index (BMI) (El-Makhzangy et al., 2010; Poorolajal & Jenabi, 2016).

2.14.3.5 Chronic Hypertension:

Women who already have hypertension during pregnancy are more prone to develop preeclampsia (Chen et al., 2017).

2.14.3.6 Diabetes:

The chance of getting preeclampsia is increased in individuals with a history of diabetes, regardless of type (Catov et al., 2007; Pankiewicz et al., 2022).

2.14.3.7 Kenal Disease:

A history of renal illness elevates the risk of developing preeclampsia (Maruotti et al., 2012).

2.14.3.8 Autoimmune Diseases:

There is an elevated risk of autoimmune illnesses, including antiphospholipid syndrome and systemic lupus erythematosus, associated with preeclampsia. (Fischer-Betz & Specker, 2017).

2.14.3.9 Family History

Preeclampsia can run in families, which can raise the risk of having the illness (Carr et al., 2005; Fischer-Betz & Specker, 2017).

2.14.3.10 Prior Stillbirth or Pregnancy Loss:

Previous experiences with stillbirths or repeated miscarriages may increase a woman's risk of getting preeclampsia in later pregnancies (Ofir et al., 2013; Rasmark Roepke et al., 2021).

2.14.3.11 Symptoms:

Symptoms of preeclampsia in women can include headaches, altered eyesight, pain in the upper abdomen, and oedema. Some people, nevertheless, might not show any obvious signs. It is significant to remember that although these characteristics can raise one's risk of preeclampsia, many cases include people who do not have these risk factors. Moreover, the presence of one or more risk factors does not ensure that preeclampsia will manifest. For all expectant persons, especially those with one or more risk factors, consistent and early prenatal care is crucial, as is constant supervision by medical professionals. Detecting and treating preeclampsia early on is essential for guaranteeing the health of the foetus and the mother.

By understanding these variables, healthcare professionals can better monitor patients and provide appropriate prenatal care by being aware of these concerns.

2. 14.4 Maternal complications from Preeclampsia

2.14.4.1 Hypertensive Crisis:

Preeclampsia is characterized by hypertension (Lambert et al., 2014), and in extreme cases, it may result in severe hypertensive episodes, such as eclampsia (characterized by seizures) and

cerebrovascular events (strokes). These acute neurological complications pose a significant threat to maternal life and require immediate medical attention.

2.14.4.2 Renal Dysfunction:

Preeclampsia often leads to impaired renal function (Sani et al., 2019), as indicated by decreased glomerular filtration rate and increased serum creatinine levels. In severe cases, renal failure can occur, necessitating renal replacement therapy.

2.14.4.3 Hepatic Dysfunction:

Impaired liver function (Chandrasekaran & Simon, 2020), characterized by elevated liver enzymes and the presence of hepatic haematoma or rupture (HELLP syndrome) (Alese et al., 2021; Zaky et al., 2004), represents a serious complication of preeclampsia. When the liver is affected, it can result in to coagulopathy and haemorrhage, (Chandrasekaran & Simon, 2020).

2.14.4.4 Cardiovascular Complications:

Preeclampsia heightens the risk of cardiovascular events, including heart failure (Melchiorre et al., 2014), myocardial infarction (Orabona et al., 2018), and pulmonary edema (Sibai et al., 1987; Wardhana et al., 2018), particularly in the postpartum period.

2.14.4.5 Disseminated Intravascular Coagulation (DIC):

DIC is a dangerous disease characterised by uncontrollably high blood clotting and haemorrhage. Preeclampsia can trigger DIC (Gomez-Tolub et al., 2022; Kobayashi & Terao, 1987), further complicating the clinical picture.

2.14.5 Foetus complications from Preeclampsia.

2.14.5.1 Preterm Birth:

Preeclampsia is a primary cause of medically indicated preterm birth (Davies et al., 2016). The condition's potential for rapid deterioration requires prompt delivery of the foetus to safeguard the mother's and the child's health.

2.14.5.2 Intrauterine Growth Restriction (IUGR):

Impaired placental perfusion in preeclampsia can lead to IUGR (Marseglia et al., 2016), leading to low birth weight and possible developmental concerns for the newborn.

2.14.5.3 Placental Abruption:

Preeclampsia heightens the likelihood of placental abruption (Lindqvist & Happach, 2006), where the placenta prematurely separates from the uterine wall. This condition can lead to foetus distress and, in severe cases, stillbirth.

2.14.5.4 Neonatal Intensive Care Unit (NICU) Admission:

Premature birth and other complications raise the chances that newborns of mothers with preeclampsia will require admission to the Neonatal Intensive Care Unit (NICU).

2.14.6 Long-term health implications of Preeclampsia:

2.14.6.1 Maternal Cardiovascular Risk:

Preeclamptic women are more likely to experience cardiovascular diseases later in life, including hypertension, stroke, and coronary artery disease. (Bokslag et al., 2017).

2.14.6.2 Metabolic Syndrome:

Preeclampsia has been linked to long-term metabolic diseases, including insulin resistance (Hu et al., 2022; Kaaja, 1998; Salzer et al., 2015; Williams, 2011), dyslipidaemia, and obesity, which are risk factors for metabolic syndrome.

2.14.6.3 Recurrence Risk:

Women with a history of preeclampsia are more prone to experience a relapse during subsequent pregnancies (Giannubilo et al., 2014; Hernández-Díaz et al., 2009).

2.14.6.4 Neurological Consequences:

Eclampsia, a severe complication of preeclampsia, can lead to long-term neurological deficits (Bartal & Sibai, 2022; Postma et al., 2014; Shah et al., 2008; Zeeman, 2009), including epilepsy and cognitive impairments.

2.14.6.5 Impact on Offspring:

Preeclamptic women may have a greater risk of hypertension in their offspring, cardiovascular issues, and metabolic disorders as they grow older, (Davis et al., 2012; Huang et al., 2021; Karatza & Dimitriou, 2020). Preeclampsia has a profound and complex effect on the mother's and the child's health. Its complications range from acute and life-threatening events to long-term health consequences that extend well beyond the perinatal period. Recognizing and managing these complications is crucial for improving results for the mother and child as well as promoting their long-term health.

2.14.7 Sociodemographic Characteristics Comparisons in Preeclampsia:

Determining the underlying causes and risk factors of preeclampsia during pregnancy requires comparing the sociodemographic characteristics of preeclamptic women to those of women with normal blood pressure. Evaluating elements like age, race/ethnicity, socioeconomic status, and education level to identify significant differences or associations is essential for uncovering the underlying mechanisms of preeclampsia. Preeclampsia incidence appears higher among women who conceive shortly after marriage (Basso et al., 2001; Robillard, Dekker, Chaouat, et al., 2019), this conundrum surrounding the disease remains, a research focus. Furthermore, research has shown a connection between preeclampsia development and maternal income and education (Bilano et al., 2014; MOSTAFA et al., 2018). A seven-fold increased risk of this disorder is linked to a birth interval longer than sixty months (Cormick et al., 2016; Wandabwa et al., 2010). The reason behind this prolonged interval and its connection to preeclampsia remains somewhat unclear, possibly stemming from factors like changes in paternity or potential subfertility, which might predispose individuals to preeclampsia. Lower socioeconomic status (Haelterman et al., 2003; Silva et al., 2008), is a complex risk factor for this condition, often linked to nutritional deficiencies, inadequate prenatal care, and poor living conditions. For instance, in India, women with lower socioeconomic status were twice as likely

to experience preeclampsia and eclampsia, (Latha & Raj, 2013). Likewise, research conducted in Australia revealed that employed women had a greater risk of developing preeclampsia and eclampsia compared to their unemployed counterparts (Najman et al., 1989), potentially due to the stress experienced during work.

2.14.8 Obstetric History Comparisons in Preeclampsia:

Women aged 40 and older face nearly double the risk of preeclampsia, regardless of whether it is their first or subsequent pregnancy, (Walker & Thornton, 2016). According to US data, the chance of developing preeclampsia increases by roughly 30% for every year that a person over 34 lives (Jawad, 2023; Ogunwole et al., 2021). On the other hand, a lower maternal age has no appreciable effect on the risk of preeclampsia.

Nulliparity is a substantial risk factor for preeclampsia, as confirmed by numerous studies (Luo et al., 2007; Myatt et al., 2012; Sibai et al., 1997). Women with preeclampsia are twice as likely to be in their first pregnancy compared to those without the condition (Funai et al., 2005). Furthermore, the risk of developing preeclampsia in a second pregnancy is seven times higher for women who experienced it during their first pregnancy (Li et al., 2014). Similarly, compared to women who did not develop preeclampsia in their second pregnancy, those who did have preeclampsia in their second pregnancy are more than seven times larger to have had it in their first pregnancy.

Preeclampsia is a disorder that is markedly more likely to run in the family; the likelihood increases by about three times if the mother, not the mother-in-law, has the ailment (Carty et al., 2010; Shamsi et al., 2013; Sutherland et al., 1981).

Regardless of chorionicity or zygosity, preeclampsia risk is almost double in twin pregnancies (Bdolah et al., 2008; Wang et al., 2021).

Additionally, triplet pregnancies have a risk of preeclampsia that is nearly three times higher compared to twin pregnancies, (Lazarov et al., 2016; Narang & Szymanski, 2021).

Pre-existing conditions notably increase the risk: insulin-dependent diabetes raises the likelihood nearly fourfold if present before pregnancy (Catov et al., 2007; Padmanabhan et al., 2017), while chronic hypertension is more common among women who develop preeclampsia (Chen et al., 2017; Shen et al., 2017). Women with superimposed preeclampsia had higher rates of perinatal complications (Chen et al., 2017; Shen et al., 2017).

Conditions like renal disease (Maruotti et al., 2012) or chronic autoimmune diseases (Fischer-Betz & Specker, 2017), elevate the risk. Antiphospholipid syndrome (Branch et al., 2001; Dreyfus et al., 2001) also heightens the risk, although no direct association was found with specific antibodies.

The interval between pregnancies significantly influences pre-eclampsia risk; 10 years or more equates to a similar risk as in nulliparous women (Shamsi et al., 2013).

Moreover, a greater BMI before becoming pregnant is a risk factor for preeclampsia (El-Makhzangy et al., 2010; Poorolajal & Jenabi, 2016). Having a high BMI, particularly over 35, greatly increases the chance of developing preeclampsia. Having a BMI above 35 at the beginning of pregnancy can double the risk of developing preeclampsia (Paré et al., 2014; Robillard, Dekker, Scioscia, et al., 2019). Women who later develop preeclampsia often exhibit higher systolic and diastolic blood pressure during the first trimester (Baschat et al., 2018). Analyzing obstetric history, including factors like parity, multiple gestations, previous preeclampsia, interpregnancy intervals, and other relevant elements can be highly valuable for preventing the onset of preeclampsia.

2.14.9 Comparative Analysis of Sociodemographic, Anthropometric, Obstetric, and Clinical differences between Preeclampsia and normal Pregnancies

Preeclampsia, a complex pregnancy-related condition affecting multiple organ systems. It is recognized by the emergence of substantial proteinuria and hypertension associated with gestation that develops after week 20 of pregnancy a woman who previously did not have these

conditions. Globally, it affects about 2-10% of pregnancies (Haque & Sarkar, 2021; Logan et al., 2020; Shamsi et al., 2013). While outcomes can be positive, it is often linked with higher maternal and perinatal health risks and mortality rates. Severe cases with early symptoms are referred to as Imminent eclampsia (Jindal et al., 2021), marked by symptoms like headache, epigastric pain, nausea, vomiting, reduced urination, and vision issues.

Eclampsia, a severe manifestation, can arise during any period of pregnancy; before, during, or after delivery. One estimate puts the percentage of maternal deaths at 10% to 15% due to preeclampsia and eclampsia (Duley, 2009; Ghulmiyyah & Sibai, 2012). The underlying cause of preeclampsia remains largely unknown, often described as a 'disease of theories' (Ekman, 2009; Lindheimer & Katz, 1981). Abnormal placentation is a key factor in its development, factors released from the compromised placenta are crucial in triggering endothelial dysfunction, a key characteristic of this condition. Interestingly, the disease can manifest without the involvement of foetus tissue, and symptoms tend to resolve post-placental delivery. Risk factors include first pregnancies, a history of preeclampsia, gestational diabetes, multiple pregnancies, connective tissue disorders, and extremes of maternal age. Management strategies carefully weigh the risks versus the benefits of inducing preterm delivery, taking into account potential complications affecting both the mother and the baby. Mild cases may be managed on an outpatient basis, initiating antihypertensive treatment at a systolic blood pressure of 150 mmHg. Severe cases necessitate stabilization and prompt delivery. Treatment involves magnesium sulfate to prevent seizures, controlling blood pressure with antihypertensives, fluid restriction, and prompt delivery. It's estimated that around 63,000 maternal deaths due to hypertensive pregnancy-related conditions occur annually (AbouZahr, 2003; Joseph, 2011), with the majority in developing nations. Complications such as eclampsia, HELLP syndrome, stroke, abruptio placentae, and pulmonary edema contribute to these fatalities. Adverse perinatal outcomes include growth restrictions, preterm births, neonatal intensive care admissions, and perinatal

deaths, necessitating close monitoring for favourable outcomes. The unpredictability of the condition's progression and the likelihood of severe complications make it challenging to foresee. Analyzing the factors leading to Imminent eclampsia is vital for improving outcomes for both mother and child. Timely administration of magnesium sulfate upon observing symptoms and considering early termination of pregnancy at hospitals are key determinants for better outcomes. Severe complications often occur in previously normotensive individuals who develop high blood pressure and imminent symptoms. This incidence is higher in countries like India (Agrawal & Walia, 2014; Magee et al., 2019), significantly impacting maternal and foetus health. Preventive measures involve proper prenatal care, early identification of preeclampsia, educating patients about imminent symptoms, and prompt management. New screening and diagnostic tools are needed to address atypical presentations for a more effective preventive strategy.

It is about time that stakeholders around the globe have a comprehensive comparative analysis between preeclampsia and normotensive pregnancies, examining various aspects including sociodemographic and pregnancy traits, hepatic and renal functions, whole blood counts, and placental and venous blood biochemistry profiles.

2.15 BLOOD CELL INDICES AND PREECLAMPSIA

Blood cell indices provide valuable insights into the physiological changes and potential complications associated with preeclampsia. These indices, which include platelet, red blood cell, and white blood cell counts, are helpful in the identification, tracking, and management of preeclampsia. The haematological profile, particularly the Complete Blood Count (CBC), can offer important insights for differentiating between preeclampsia and normal pregnancy (Bulbul et al., 2021; Ceyhan et al., 2006; Kirbas et al., 2015; Örgül et al., 2019). In a typical CBC comparison between preeclampsia and normal pregnancy, several key differences stand out;

Preeclampsia frequently presents with changes in several CBC parameters when compared to normal pregnancy (Ceyhan et al., 2006). Preeclampsia frequently presents with lower levels of haemoglobin and haematocrit in contrast to a typical pregnancy (Elgari et al., 2019). This decline may be indicative of anaemia, which can be exacerbated in severe cases of preeclampsia. Moreover, Platelet count tends to decrease in preeclampsia (Dadhich et al., 2012; Nooh & Abdeldayem, 2015), which is not universally observed, thrombocytopenia can occur especially in cases of severe preeclampsia. This can result in a higher risk of bleeding complications.

In preeclamptic women, there is frequently a slight rise in white blood cell count, particularly lymphocytes (Elgari et al., 2019), however, this elevation usually remains within the normal range or slightly above, often as a response to inflammation or infection. Furthermore, there are alterations in Red Blood Cell (RBC) Indices (Elgari et al., 2019). It is possible to find changes in the red blood cell indices mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC). If anaemia is present, these changes can provide information on the type of anaemia.

In preeclampsia, there is a decreased reticulocyte count (Elgari et al., 2019). This could be indicative of ineffective erythropoiesis, contributing to reduced haemoglobin levels. Additionally, peripheral blood smear examination of the blood smear may reveal abnormalities such as schistocytes or fragmented red blood cells, suggestive of microangiopathic haemolysis, a feature sometimes seen in severe cases of preeclampsia (Adewoyin, 2014; Moreno & Menke, 2002). These haematological differences between preeclampsia and a normal pregnancy can assist clinicians in diagnosing and managing the condition. However, it is crucial to recognize that not all preeclampsia cases exhibit these changes, and individual differences may occur. Therefore, a comprehensive assessment, including clinical history and other diagnostic parameters, is crucial for accurate diagnosis and appropriate management.

2.15.1 Haemoglobin and Haematocrit:

Comparing haemoglobin and haematocrit values in preeclamptic women as opposed to those in pregnancies without hypertension reveals lower levels in the disease condition (Elgari et al., 2019).

The difference is due to anaemia in preeclampsia.

2.15.2 Platelet Count:

Platelet counts in preeclampsia are low as compared with normal pregnancy (Dadhich et al., 2012; Nooh & Abdeldayem, 2015), which sometimes leads to thrombocytopenia, a condition characterized by low platelet levels.

2.15.3 White Blood Cells Count:

Among preeclampsia pregnancies, there are low levels of neutrophils accompanied by elevated lymphocyte counts (Elgari et al., 2019).

The identification of predictive markers for preeclampsia is of great interest in obstetrics, and one such marker under investigation is the white blood cell (WBC) count and its immunological implication in preeclampsia. We investigate the potential marker function of white blood cell count for preeclampsia and its clinical significance in this section.

2.16 IMMUNOLOGY IN PREECLAMPSIA:

Preeclampsia is linked to systemic inflammation and immune dysregulation. The placental implantation process triggers an inflammatory response, which, in preeclampsia, can become excessive and contribute to the development of the condition.

Immune cells, such as white blood cells, hold diagnostic value in this pregnancy condition.

2.16.1 White blood cells (WBCs);

White blood cells, or WBCs, are vital components of the immune system and are involved in the inflammatory response of the body (Elgari et al., 2019). Increased levels of WBCs may reflect an underlying inflammatory state.

2.16.2 Neutrophils and Monocytes;

White blood cell counts (including neutrophils, eosinophils, basophils, monocytes, and lymphocytes) between preeclamptic and normotensive pregnant women have not been shown to differ significantly, (Elgari et al., 2019; Lurie et al., 1998), one study did find elevated neutrophil levels in severe preeclampsia compared to mild cases (Lurie et al., 1998). Eosinophil counts might have predictive value for preeclampsia (Adewoyin, 2014), Monocytes have been linked to the pathogenesis of preeclampsia by inducing oxidative stress and inflammation, which are variables that contribute to endothelial dysfunction and hypertension (Vishnyakova et al., 2019). Elevated neutrophil and monocyte counts have been observed in some individuals with preeclampsia, (Luppi & DeLoia, 2006; Lurie et al., 1998; Melgert et al., 2012; Vishnyakova et al., 2019).

2.16.3 Predictive Value of WBCs:

According to research, having a high white blood cell count during pregnancy, especially in the early stages, may be a sign of preeclampsia later on (Kirbas et al., 2015; Liao et al., 2022).

An increased white blood cell count during routine prenatal blood tests may raise suspicion of preeclampsia. It can be indicative of an underlying inflammatory response that might predispose the individual to the condition.

2.16.4 Clinical Significance of WBC Prediction:

While an elevated white blood cell count can be a potential predictor, however, It can be affected by a variety of circumstances, such as infections and other inflammatory disorders, and is not exclusive to preeclampsia (Honda et al., 2016). Healthcare providers typically use a

combination of clinical and laboratory assessments, including blood pressure measurements and proteinuria, to diagnose preeclampsia.

2.16.5 Clinical Utility of blood cell indices for monitoring and management of preeclampsia:

Regular monitoring of white blood cell count during prenatal care is essential. If a pregnant individual exhibits persistently elevated white blood cell counts, healthcare providers may investigate potential underlying causes and assess for signs of preeclampsia.

The main diagnostic criteria for preeclampsia are hypertension and proteinuria, but elevated white blood cell counts can be considered as part of the overall clinical picture. Elevated white blood cell count can be indicative of an underlying inflammatory state (Aneman et al., 2020), which could be linked to the onset of preeclampsia.

While it can serve as a predictor, it is not a stand-alone diagnostic tool for preeclampsia. Early prenatal care, comprehensive monitoring, and the assessment of multiple clinical and laboratory parameters, including blood pressure and proteinuria, remain essential for the accurate diagnosis of preeclampsia and the provision of timely medical care to affected individuals.

2.17 PREECLAMPSIA AND BIRTH WEIGHT: A PLACENTA FUNCTION

The placenta serves as a conduit for the delivery of nutrients and connects the developing foetus to the uterine wall, and waste removal, and facilitates gas exchange through the mother's blood. Its unique function holds crucial significance and not only affects the outcomes of the pregnancy but also has implications for the child's long-term health (Godfrey, 2002; Longtine & Nelson, 2011). The placenta significantly influences and directly correlates with reducing pregnancy complications, encompassing maternal and foetus disorders, clinical issues, and gestational duration (Burton et al., 2016). Its function profoundly impacts the well-being of the foetus and newborn, including factors like placental structure, blood flow, and nutrient transfer, pivotal in the foetus growth trajectory (Godfrey, 2002). At birth, a baby's weight serves as a reliable

indicator of their health and that of the mother (Conley & Bennett, 2000). Lower birth weight raises the risk of infant mortality and can lead to weakened immune function in some survivors (Taylor, 2016), It may also result in lower IQ, impaired cognitive skills, and an increased likelihood of developing conditions such as diabetes, blood pressure, and in later life; coronary artery disease (Gunnarsdottir et al., 2002; Mohseni et al., 2020). A birth weight of less than 2,500 grams is considered low birth weight by the World Health Organisation (Organization, 2006b), affecting approximately 16 percent of all global births in 2013, and around 22 million newborns. However, accurate birth weight monitoring remains challenging, with nearly 50% of newborns worldwide not having their birth weight recoded (Blencowe et al., 2019; Lawn et al., 2010). An estimated 5 million newborn fatalities occur annually as a result of low birth weight and have implications for impaired adult well-being (Brown & Eisenberg, 1995; Perera, 2018). This includes the hypothesis linking low birth weight with hindered postnatal growth and overall health (Perera, 2018). Being the only organ that connects the mother to the baby, is crucial for ensuring a healthy baby by facilitating the transfer of nutrients, gases, waste, heat, hormones, and regulatory molecules. Extremely small or premature babies face increased risks of mortality and various morbidities, notably neurological, respiratory, and gastrointestinal diseases (Tan et al., 2014), where placental characteristics determine foetus development and future disease patterns. This particular study in Ghana, known for its commendable health accomplishments akin to developed nations, aims to explore the impact of placental weight, volume, surface area, and thickness across various birth weight categories on gestational age. Ghana has reported severally, higher prevalence rates of low birth weight across the country (Abubakari et al., 2015b; Agorinya et al., 2018; Axame et al., 2022), compared to other developed countries, driving this study to explore the prevalence of low birth weight infants and the role of the placenta in their development. The insights from placental morphometry could

offer protective factors against low birth weight, enhancing prenatal care for both mother and foetus.

2.18 OVERVIEW OF OXIDATIVE STRESS AND PREECLAMPSIA

Twelve major clusters, each containing a variety of unique cell types, make up the human placenta (Liu et al., 2018). Stromal cells, endothelial cells, extravillous trophoblasts (EVT), and villous cytotrophoblasts (CTV) are important cell types. One prominent cell form that results from the fusion of villous trophoblasts is the syncytiotrophoblast (SCT) (Huppertz & Gauster, 2011; Renaud & Jeyarajah, 2022), stands out from the trophoblast lineage. These cells produce mRNA encoding the Chorionic Gonadotrophin β polypeptide (Acevedo et al., 1995; Hussa, 1980), Human Chorionic Gonadotrophin hormone (hCG), produced by the placenta soon after eight days of fertilisation, during implantation and syncytialization, is a critical component in early pregnancy. Immune cell clusters, such as macrophages, T lymphocytes and dendritic cells have been seen in the placenta and they might contribute to oxidative stress (Ortiz et al., 2013). Low or high oxygen concentrations, as well as changes in hypoxia and reoxygenation, can cause oxidative stress, particularly in highly vascularised tissues such as the brain or eyes (Li et al., 2012; Opichka et al., 2021; Shah & Khalil, 2015).

In a healthy placenta, hypoxia is typically present during early pregnancy (Burton et al., 2021; Soares et al., 2017; Zhao et al., 2021), complicating the differentiation between normal physiological changes and potential pathological conditions at various stages of placental development. Oxidative stress in the placenta can originate from trophoblast cells, endothelial cells (ECs) in the placental tissue, stromal cells in the villi, or immune cells like Hofbauer cells. Generally, oxidative stress impacts trophoblasts by altering gene expression.

Preeclampsia is strongly linked to oxidative stress (Agarwal et al., 2012; Siddiqui et al., 2010), which arises from an imbalance between the production of reactive oxygen species (ROS) and

the body's ability to neutralize their effects. This imbalance is central to the pathophysiology of preeclampsia (Siddiqui et al., 2010), and is significant in various health issues, including reproductive disorders and pregnancy complications (Agarwal et al., 2012). Increased oxidative stress during pregnancy is associated with immune system changes, leading to higher ROS levels (Al-Gubory et al., 2010; Duhig et al., 2016). The placenta is considered a primary source of ROS during gestation (Duhig et al., 2016; Myatt & Cui, 2004).

Naturally, antioxidants keep ROS in check, but when ROS levels exceed antioxidants, oxidative stress occurs. Gestational diabetes and hypertensive diseases are two adverse consequences associated with increased oxidative stress during pregnancy for both the mother and the foetus (Phoswa & Khaliq, 2021). This problem is particularly severe in developing countries, where hypertensive disorders during pregnancy are more common (Firoz et al., 2011; Ratsiatosika et al., 2019), leading to significantly higher maternal mortality rates compared to developed nations.

Endothelial dysfunction can be caused by risk factors such as obesity, insulin resistance, and excessive cholesterol, which can promote oxidative stress and inflammation. However, the exact mechanisms linking these factors to conditions like preeclampsia remain not fully clarified. In preeclampsia, inadequate trophoblast invasion and insufficient remodeling of the uteroplacental arteries are associated with hypoxia, increased reactive oxygen species (ROS), and endothelial dysfunction (Opichka et al., 2021; Shah & Khalil, 2015).

Investigating the preeclampsia's oxidative stress pathways, biomarkers used to assess its presence, and the role of antioxidant defense mechanisms in mitigating oxidative damage will be the key focus of the discussion.

2.19 OXIDATIVE STRESS MECHANISMS:

While the precise aetiology of preeclampsia is yet unknown, insufficient remodelling of the mother's blood vessels that supply the intervillous space in the placenta significantly contributes to the development of this condition (Boeldt & Bird, 2017; Opichka et al., 2021). This deficiency can cause a complex cycle of ischaemia and reperfusion within the placenta, releasing harmful substances into the mother's bloodstream. (Boeldt & Bird, 2017; Gilbert et al., 2008; Zárate et al., 2014). The placenta's fluctuation between low oxygen levels and reoxygenation, known as hypoxia/reoxygenation, is associated with disrupted angiogenesis, damage to blood vessel linings, cardiovascular issues, and an intensified inflammatory response (Opichka et al., 2021; Shah & Khalil, 2015).

In preeclampsia, the alternating low oxygen and reoxygenation in the uteroplacental region heightens oxidative stress and impacts the health of the foetus as well as the mother. Stress due to oxidation in preeclampsia arises from multiple interconnected mechanisms:

2.19.1Placental Ischaemia-Hypoxia:

In preeclampsia, inadequate blood circulation to the placenta causes placental ischaemia and hypoxia, (Barrientos et al., 2017; Opichka et al., 2021; Shah & Khalil, 2015). This state of reduced oxygen and blood flow results in elevated levels of reactive oxygen species (ROS) in the mother's circulation and placenta.

2.19.2 Activation of Inflammatory Pathways:

Inflammatory processes can be triggered by oxidative stress (Gill et al., 2010), causing an inflammatory response. This inflammatory state contributes to endothelial dysfunction and organ damage (Steyers III & Miller Jr, 2014; Theofilis et al., 2021; Zhang, 2008), particularly in the kidneys and liver.

2.19.3 Inflammatory Response:

Preeclampsia involves a widespread inflammatory reaction characterized by immune cell activation and the release of cytokines that promote inflammation (Gilbert et al., 2008; Poston, 2006). This inflammatory response can begin the process of reactive oxygen species production (ROS).

2.19.4Endothelial Dysfunction:

ROS impair endothelial function, leading to vasoconstriction and reduced blood flow (Incalza et al., 2018). Dysfunction of the vascular endothelium (Wu et al., 2015), a hallmark of preeclampsia, disrupts nitric oxide (NO) production, reducing its antioxidant properties and contributing to oxidative stress. This endothelial dysfunction contributes to hypertension, a hallmark of preeclampsia.

2.19.5 Oxidative Stress Feedback Loop:

Oxidative stress can intensify damage to endothelial cells, (Schoots et al., 2018) resulting in a rise in ROS production and creating a detrimental cycle that perpetuates further harm.

2.19.6 Oxidative damage:

Increased reactive oxygen species (ROS) can cause oxidative damage to lipids, proteins, and DNA, which exacerbates tissue damage and cellular dysfunction in both the foetal and maternal systems (Burton et al., 2003).

2.20 BIOMARKERS OF OXIDATIVE STRESS:

Accurately assessing oxidative stress in preeclampsia relies on reliable biomarkers. Commonly used biomarkers include:

2.20.1 Malondialdehyde (MDA):

MDA is a result of lipid peroxidation and a well-known biomarker for oxidative stress, a process that occurs when ROS damage cell membranes. Elevated MDA levels in maternal blood or urine can indicate increased oxidative stress in preeclampsia, MDA is used to assess lipid peroxidation (Grotto et al., 2009; Niki, 2014; Spirlandeli et al., 2013; Tsikas, 2017). Increased MDA concentrations, a crucial indicator of oxidative stress, signal heightened oxidative damage to lipids in cases of preeclampsia.

2.20.2 Total Antioxidant Capacity (TAC):

A biological sample's total antioxidant capacity (TAC) is determined; lower results suggest a reduced potential to resist oxidative damage (Gedikli et al., 2009; Suresh et al., 2009). Those with preeclampsia often exhibit reduced TAC, indicating diminished antioxidant defenses (Dirican et al., 2008).

2.20.3 Catalase (CAT):

An antioxidant enzyme called catalase helps hydrogen peroxide break down into oxygen and water. Oxidative stress may be indicated by decreased catalase activity (Escribano et al., 2015).

2.20.4 The Oxidative Stress Index (OSI):

OSI is a marker that quantifies this imbalance (Sánchez-Rodríguez & Mendoza-Núñez, 2019), and its utility in preeclampsia has gained attention in recent research. In this context, we examine the importance of OSI in preeclampsia:

Quantifying Oxidative Stress: OSI is an index used to quantify oxidative stress within the body (Sánchez-Rodríguez & Mendoza-Núñez, 2019). It assesses how well reactive oxygen species (ROS) and antioxidants, offering a more comprehensive assessment of the oxidative status compared to measuring individual markers alone.

Diagnostic Potential: Preeclampsia is linked to heightened oxidative stress, and evaluating OSI can serve as an important instrument for early diagnosis and detection. Increased OSI levels can indicate the oxidative burden in those affected.

Monitoring: OSI in pregnant individuals at risk for or already diagnosed with preeclampsia can aid in the timely identification of the condition, allowing for prompt management and intervention.

Predictive Value: Research has demonstrated that elevated OSI levels during the early stages of pregnancy might be indicative of the likelihood of developing preeclampsia later on (Gupta et al., 2005; Perrone et al., 2019). This predictive potential can aid in identifying those at high risk and requires more careful observation and specialized care.

Prognostic Significance: In individuals already diagnosed with preeclampsia, OSI can serve as a prognostic marker. Increased levels of OSI could indicate the severity of the condition and the probability of experiencing complications (Gupta et al., 2005).

Measuring OSI; measuring OSI during pregnancy can assist healthcare providers in tailoring treatment plans and making decisions regarding the timing of delivery, especially in cases of severe preeclampsia.

Monitoring Treatment Efficacy: Monitoring OSI levels during treatment can help evaluate the effectiveness of interventions aimed at reducing oxidative stress and managing preeclampsia.

A reduction in OSI; may indicate a positive response to treatment, guiding healthcare providers in adjusting therapeutic strategies.

Research and Therapeutic Development: Examining OSI in preeclampsia enhances our understanding of the condition's pathophysiology (Gupta et al., 2005), and can aid in the creation of fresh treatment plans that address oxidative stress as part of the treatment plan.

Lifestyle and Nutritional Interventions: Modifying lifestyle and nutritional factors that influence oxidative stress can help manage preeclampsia. Dietary changes, including the consumption of antioxidants, may be recommended based on OSI levels.

Limitations and Considerations: While OSI is a valuable marker, it should be interpreted alongside other clinical and laboratory parameters, such as blood pressure, proteinuria, and the individual's overall health.

There is no single "gold standard" for measuring OSI, and different methods may yield slightly different results, making standardization an ongoing area of research. The Oxidative Stress Index (OSI) is crucial for assessing and managing preeclampsia. It provides a useful means for early detection, prediction, and prognosis of the condition. Monitoring OSI levels can guide healthcare providers in tailoring treatment strategies and improving outcomes for pregnant individuals with preeclampsia. However, it is essential to consider OSI results in the context of comprehensive clinical assessments to make knowledgeable choices about preeclampsia diagnosis and treatment.

2.21 ROLE OF ANTIOXIDANT DEFENSE MECHANISMS:

2.21.1 Endogenous Antioxidants:

The body possesses a sophisticated antioxidant defense network featuring enzymes like SOD, GPx, as well as non-enzymatic antioxidants including glutathione, vitamins C and E, and Catalase. These antioxidants function in tandem to protect cells from harm and neutralise reactive oxygen species (ROS) (Jeeva et al., 2015) (He et al., 2017). In cases of preeclampsia, decreased enzyme activity may make it more difficult for the body to adequately fight oxidative stress in preeclamptic instances.

2.21.2 Placental Antioxidant Capacity:

To defend the growing foetus, the placenta possesses its own antioxidant defence systems. Increased oxidative stress, a contributing cause to preeclampsia, can result from disruptions to these processes (Al-Gubory et al., 2010; Aouache et al., 2018; Schoots et al., 2018). Understanding oxidative stress and the indicators that are linked to it, is essential for the timely identification and treatment of preeclampsia. Furthermore, studying the regulation of antioxidant defence systems may aid in the creation of therapies that lessen the negative consequences of oxidative stress in this pregnancy illness.

2.21.3 Dietary Antioxidants:

Diets rich in antioxidants, such as those high in vitamins C and E, may help in lowering oxidative stress in pregnant women.

As per several studies (Conde-Agudelo et al., 2011; Poston et al., 2011; Suhail et al., 2008; Tenório et al., 2018; Xu et al., 2010), their function in averting preeclampsia is still being studied. Vitamins C and E are among these non-enzymatic antioxidants that help shield cellular components (Varesi et al., 2023). Understanding oxidative stress mechanisms, identifying relevant biomarkers, and assessing antioxidant defenses are critical for deciphering the pathophysiology of preeclampsia. Targeted interventions to mitigate oxidative stress may hold promise for the prevention and management of this complex pregnancy disorder.

2.21.4 Oxidative stress and placenta formation.

For a human pregnancy to progress healthily, trophoblast cells and uterine vessels must develop properly. First, a layer of mononucleated cytotrophoblasts (CTBs) surrounds the blastocyst. After adhering to the endometrium, these cells proliferate quickly, developing into invasive extravillous trophoblasts (EVTs) that pierce the uterine stroma with the inner cluster and multinucleated syncytiotrophoblasts (STBs) in the outer layer. The "two-wave invasion" theory

states that a second wave of deeper and more comprehensive invasion starts around week 12 of gestation, after the first invasion occurs in the decidual layer and there is a halt (San Juan-Reyes et al., 2020; Wu et al., 2015). In this latter phase of invasion, maternal spiral arteries are enhanced by EVTs that have extensively invaded the endometrium in order to create low-resistance maternal-foetus circulation and secure the foetus, both interstitial and endovascular penetration are essential. Preeclampsia (PE) and intrauterine growth restriction (IUGR) are related to insufficient trophoblast invasion, particularly during the second wave, (Barrientos et al., 2017). Events involving ischaemia/reperfusion (I/R) may be associated with this impairment. The generation of reactive oxygen species (ROS) from these sources results; in the inactivation of biomacromolecules, endothelial dysfunction, trophoblast apoptosis, disruption of cellular metabolism, and a rise in factors that inhibit angiogenesis, like sFlt-1 and sEng. These factors neutralize proangiogenic factors in the maternal circulation, such as VEGF and TGF-β1. (Wu et al., 2015). An increase in blood supply and the progression of trophoblast differentiation are linked to changes in placental oxygen level(Chang et al., 2018; James et al., 2006).

Low oxygen levels occur in the placental intervillous area before week 10 of human gestation. (Genbacev et al., 1997). Doppler ultrasounds and morphological analyses reveal a non-haemochorial placenta during this time, with trophoblast cells blocking the uteroplacental arteries at their tips (Ackerman IV et al., 2014). By the end of the first trimester, these blocks progressively disappear as the second wave of trophoblast invasion takes place, and causes the placental oxygen partial pressure to rise significantly from <20 mmHg at week 8 to >50 mmHg at week 12 (San Juan-Reyes et al., 2020; Wu et al., 2015). This rise causes trophoblasts to experience increased oxidative stress (OS). Interestingly, blood and OS enter the placenta in the periphery and spread outward with time, (Wu et al., 2015; Zhao et al., 2021). This slow, peripheral-to-central diffusion of OS protects the foetus against an abrupt increase in OS while also causing the chorion frondosum to degrade and create the chorion leave, (Guo, 2020), This

can result in early pregnancy failure. Vascular and trophoblastic biological characteristics are intimately correlated with placental OS, influencing each other's development and variability. Differentially yet equally important for endothelial development at different periods of gestation are VEGF and PlGF. ROS from first trimester low oxygen and prolonged hypoperfusion induce VEGF expression through HIF-1, (San Juan-Reyes et al., 2020). On the other hand, while PlGF rises with increasing oxygen levels, VEGF is later downregulated by high oxygen, (Upalakalin et al., 2002). In the first trimester, VEGF induces endothelial migration and proliferation, but in the second and third trimesters, PlGF encourages non-branching angiogenesis. Early in pregnancy, hypoxia and premature haemo-perfusion may lower VEGF levels and create an early PlGF peak, which may interfere with normal vascular development and result in pregnancy failure, (Mehta, 2011). In addition to being signaling molecules, ROS also cause angiogenesis utilizing growth factor-independent mechanisms, (Semenza, 2009). They can create carboxyalkyl pyrroles (CAPs), which bind to endothelial cells' Toll-like receptors (TLRs) and stimulate neovascularisation, (Malinin et al., 2011). Specifically, OS-induced Ataxia-Telangiectasia Mutated (ATM) kinase promotes pathological neoangiogenesis, (Huang & Nan, 2019). But high OS, insufficient scavenging systems, and vascular aging are linked to conditions including hypertension and atherosclerosis, (Izzo et al., 2021). Peroxidized lipids, which are byproducts of oxidative stress, are linked to pathological angiogenesis and atherogenic processes, (Gianazza et al., 2021; Negre-Salvayre et al., 2010). Reduced artery diameter and elevated plasma OS biomarkers are two similar vascular changes to atherosclerosis that appear in the placenta of IUGR patients, (Odame Anto et al., 2018). OS oxidizes NO straight to ONOO−, decreasing NO availability and increasing the risk of thrombosis, inflammation, and constriction in arteries. Moreover, OS dissociates eNOS, producing ONOO− and lowering the bioavailability of NO, (Busse & Fleming, 1996). According to experimental studies, CTBs cultured in low oxygen concentrations primarily multiply, demonstrating poor differentiation

and invasion capabilities, whereas CTBs cultured in high oxygen concentrations stop proliferating yet allow normal differentiation, (Wu et al., 2015). This points to changes that occur in trophoblast cells in vivo, where low oxygen levels during the first trimester may encourage proliferation while preventing invasion and differentiation. The secondary trophoblast invasion wave may then depend on CTBs transitioning from an extravillous proliferative phenotype to an invasive one as a result of an OS surge. OS modifies trophoblast cells' integrin patterns, (Wu et al., 2015). Hypoxia upregulates the α5 or α6/β1 integrin subunits but suppresses the expression of CTB α1/β1 integrin, (Lyall, 1998; Wu et al., 2015), increasing placental development and generally influencing CTB conversion to the extravillous phenotype. In EVT cells, hypoxia also suppresses Matrix Metalloproteinases (MMPs) such as MMP-2, while a well-oxygenated environment promotes EVT cell invasion by activating MMP-2, MMP-9, and α1 integrins, (Wu et al., 2015).

MMPs and integrins are probably regulated by HIF-1 and TGF-β3. HIF-1 stimulates CTB proliferation in response to low oxygen levels, but inhibits invasion and differentiation, (Chang et al., 2018). Reduced HIF-1 causes a drop in TGF-β3, which in turn activates MMPs and modifies integrin isoforms when placental O_2 levels rise. Abnormal integrin α1 and MMP-9 levels in trophoblasts hinder placental blood perfusion and EVT penetration in situations similar to PE, (Lockwood et al., 2014). CTBS must be able to merge into STBs for the exchange of materials and the manufacture of hormones throughout foetal development. Reduced production of hormones like hCG, hPL, and pGH, which are markers of well-differentiated STBs, results from overexpression of SOD, which inhibits CTBs' capacity to fuse into STBs, (Bischof & Irminger-Finger, 2005; Fisher et al., 2015). Pregnancies classified as PE or IUGR show higher apoptosis and decreased cell fusion. Knowing the CTB fusion processes and how they interact with the redox system may help explain anomalous placentation.

2.22 OXIDATIVE STRESS AND THE PATHOGENESIS OF PREECLAMPSIA

In pregnancies with normal blood pressure as well as in those affected by preeclampsia, blood pressure patterns undergo distinct variations (Benedetto et al., 1996), but the patterns and severity of fluctuations differ significantly. Blood pressure in normotensive pregnancies generally remains within normal ranges throughout gestation (Hermida et al., 2000), with a few minor adjustments. During the first trimester, blood pressure may drop somewhat; by the third trimester, it will progressively restore to pre-pregnancy values. High blood pressure is a hallmark of preeclampsia after 20 weeks of pregnancy which frequently exceeds 140/90 mmHg, (August & Sibai, 2017). Blood pressure fluctuations in preeclampsia can be erratic, with sudden spikes or a continuous rise in severity. In preeclampsia, this is manifested in varying degrees of severity. Initially, blood pressure elevation might be mild, but it can progress rapidly to the severe stage. This stage presents with more pronounced hypertension, often accompanied by other symptoms like proteinuria, severe headaches, visual disturbances, and organ dysfunction (August & Sibai, 2017). In preeclampsia, oxidative stress indicators and hypertension are directly correlated (Bernardi et al., 2008). In preeclampsia, the level of hypertension is closely associated with indicators of oxidative stress, such as increased reactive oxygen species (ROS) or lowered antioxidant levels, (Llurba et al., 2004; Turpin et al., 2015). The degree of oxidative stress increases with the severity of preeclampsia. Persistent oxidative stress causes endothelial dysfunction as a result of the link between oxidative stress and hypertension, (Turpin et al., 2015). This contributes to endothelial dysfunction, impairing blood vessel dilation and leading to increased resistance in vessels, thereby elevating blood pressure. Moreover, the presence of higher oxidative stress intensifies the inflammatory response (Lugrin et al., 2014), affecting blood vessel integrity and contributing to vasoconstriction, further elevating blood pressure. This intends to result in disruption of placental function, restricting the foetus's blood supply. The severity of hypertension in preeclampsia is influenced by the impaired placental circulation

(Rana et al., 2019). It is significant to highlight the correlation between oxidative stress markers and the severity of hypertension in preeclampsia (Oztas et al., 2016). Oxidative stress plays a crucial role in the complex dynamics of blood pressure increase in preeclampsia and negatively impacts endothelial health and vascular function. Understanding this connection helps to expand the range of potential treatments for this condition. Oxidative stress, marked by an imbalance between free radicals and antioxidant defences, contributes to endothelial dysfunction and vasoconstriction, which are closely associated with preeclampsia (Guerby et al., 2021). Abnormal levels of oxidative stress upset the delicate equilibrium of endothelial function, compromising the release of vasoactive substances like nitric oxide (NO), which typically regulate blood vessel dilation. Elevated oxidative stress levels promote vasoconstriction by diminishing the bioavailability of NO (Clapp et al., 2004; Gracia-Sancho et al., 2008), increasing the production of endothelin-1 and the renin-angiotensin-aldosterone system (RAAS), (Rossi et al., 1999), which eventually results in higher blood pressure and peripheral resistance.

Elevated blood pressure, typical in preeclampsia, leads to increased mechanical stress on blood vessel walls, resulting in endothelial damage and oxidative stress afterward, malfunctioning endothelium induced by oxidative stress perpetuates hypertension (Watson et al., 2008). Dysfunctional endothelium loses its ability to regulate blood vessel tone and maintain homeostasis, further elevating blood pressure. Endothelial dysfunction, influenced by oxidative stress, compromises the delicate balance between vasodilation and vasoconstriction, favouring the latter and contributing to hypertension in preeclampsia (Possomato-Vieira & Khalil, 2016; Taylor et al., 2009). Recognising the critical roles played by oxidative stress and endothelial dysfunction creates opportunities for possible therapeutic approaches (Feng et al., 2021), techniques to lower oxidative stress in preeclampsia, and enhanced endothelial function may be able to regulate blood pressure. Antioxidants such as vitamins C and E, which focus on reducing

oxidative stress, may enhance endothelial function and lower blood pressure in preeclamptic patients. Therapies enhancing NO bioavailability (Kurowska, 2002), like NO donors or supplements, aim to counteract the vasoconstrictive effects induced by oxidative stress, thereby mitigating blood pressure elevation. There seems to exist a bidirectional relationship between blood pressure elevation and oxidative stress, especially when endothelial dysfunction is present, which provides crucial insights for developing targeted therapies for managing hypertension in preeclampsia. There is substantial therapeutic potential in addressing the problems linked to high blood pressure in this disease by using strategies on reducing oxidative stress and restoring endothelial function.

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2.23 THE BIDIRECTIONAL EFFECT BETWEEN OXIDATIVE STRESS AND BLOOD PRESSURE.

In preeclampsia, there is a complicated relationship between oxidative stress and blood pressure (Phoswa & Khaliq, 2021), Markers reveal a significant interplay that contributes to the condition's pathophysiology. Preeclampsia is characterized by high blood pressure, and while the relationship between oxidative stress and blood pressure is complex, oxidative stress plays a crucial role in its development. Oxidative stress, characterised by an imbalance between antioxidants and free radicals, is a major cause of preeclampsia. Oxidative stress in this state is a result of both decreased antioxidant defences and a rise in the production of ROS, or reactive oxygen species. In preeclampsia, oxidative stress and elevated blood pressure have a reciprocal link, (Crowley, 2014). Endothelial dysfunction brought on by oxidative stress causes vasoconstriction and lower nitric oxide bioavailability, (Clapp et al., 2004). Nitric oxide is essential for maintaining blood vessel dilation and normal blood pressure regulation. Reduced nitric oxide levels due to oxidative stress cause blood vessels to constrict, increasing blood pressure.

Conversely, elevated blood pressure in preeclampsia can further promote oxidative stress (Chiarello et al., 2020; Hubel, 1997). Hypertension exerts mechanical stress on blood vessel walls, leading to increased ROS production (Hirata & Satonaka, 2001; Schiffrin, 2020; Virdis et al., 2011). The stressed endothelium releases signals that trigger inflammatory responses, amplifying oxidative stress and creating a cyclical relationship where high blood pressure induces oxidative stress, which exacerbates hypertension.

Quantifying the association between oxidative stress markers in circumstances like preeclampsia and blood pressure measurements could be of use in these circumstances. The utilization of correlation studies is necessary for measurements like systolic and diastolic blood pressure. Due to vascular dysfunction in preeclampsia, these measurements, which are essential markers of cardiovascular health, often exhibit notable elevations (Opichka et al., 2021; Tenório et al., 2019). Lipid peroxidation products, reactive oxygen species (ROS) (such as malondialdehyde, or MDA), antioxidant enzymes (such as superoxide dismutase or SOD, catalase), and TAC are examples of markers of oxidative stress that are frequently evaluated to determine the degree of oxidative stress in preeclampsia. Statistical methods such as Pearson's correlation coefficient and Spearman's rank correlation are employed to measure both the strength and direction of the relationship between blood pressure data and oxidative stress markers. A positive correlation indicates that as blood pressure levels rise, oxidative stress marker levels tend to increase. Conversely, a negative correlation suggests that elevated blood pressure coincides with reduced oxidative stress marker levels. The correlation coefficient's value reveals how strong the relationship is; values closer to 0 indicate a weaker or insignificant relationship, whereas values closer to 1 or -1 indicate a strong relationship. Correlation analyses aid in understanding the mechanistic links between blood pressure and oxidative stress in conditions like preeclampsia, shedding light on disease progression, potential therapeutic targets, and the pathophysiology of the disease condition. Finding a significant positive relationship between oxidative stress

indicators and blood pressure can serve as a predictive marker (Rodrigo et al., 2013). Higher oxidative stress levels alongside elevated blood pressure might indicate increased disease severity. Insights derived from correlation analyses can guide the development of interventions targeting oxidative stress to manage blood pressure in preeclampsia. Strategies that reduce oxidative stress could potentially help control hypertension in affected pregnancies. Correlation analyses, therefore, offer important new perspectives on the connection between oxidative stress markers and blood pressure readings. They offer a quantitative viewpoint on the interactions between these variables in preeclampsia, which aids in the comprehension, prognostication, and treatment of this complicated illness. Oxidative stress and elevated blood pressure combine to worsen vascular damage, his influences both the mother's and the foetus's health.

Persistent oxidative stress harms blood vessels, disrupts placental circulation, and It restricts the foetus's access to nutrients and oxygen, (Schoots et al., 2018; Wu et al., 2015). This impaired placental function can lead to foetus growth restriction and various pregnancy complications. Comprehending the complex correlation between oxidative stress indicators and blood pressure is crucial in order to formulate possible treatment strategies. Antioxidant therapies or strategies aimed at reducing oxidative stress could potentially help mitigate the endothelial dysfunction and blood pressure elevation seen in preeclampsia. However, due to the complex nature of the condition, interventions targeting a single pathway might have limited efficacy. The connection between blood pressure elevation and oxidative stress markers in preeclampsia is mutually reinforcing. Oxidative stress contributes to hypertension, while high blood pressure intensifies oxidative stress, creating a detrimental cycle that significantly impacts maternal and foetus health in preeclamptic pregnancies. Blood pressure regulation is a complicated physiological process, and medical study must focus on how it relates to signs of oxidative stress.

2.23.1 Oxidative Stress and Hypertension:

Hypertension is one known risk factor for cardiovascular diseases, such as heart attacks and strokes (Kjeldsen, 2018). Research has conclusively shown a connection between oxidative stress and high blood pressure (Nabha et al., 2005; Ward & Croft, 2006).

Excessive generation of ROS due to chronic hypertension might harm blood vessels and causes endothelial dysfunction, further contributing to elevated blood pressure.

2.23.2 Oxidative Stress and Endothelial Dysfunction:

Oxidative stress (ROS) has a direct effect on the endothelium, the inner lining of blood vessels. ROS can damage endothelial function by lowering the bioavailability of nitric oxide (NO), a molecule that is crucial for modulating blood vessel tone (Schulz et al., 2011). Vasoconstriction and increased vascular resistance are caused by reduced NO availability, and these events raise blood pressure.

2.23.3 Oxidative Stress and Renin-Angiotensin-Aldosterone System (RAAS):

One important blood pressure regulator is the renin-angiotensin-aldosterone system (RAAS) (Muñoz-Durango et al., 2016). Oxidative stress might cause the RAAS to become hyperactive.

2.23.4 Oxidative Stress and Inflammation:

Inflammation, which is closely associated with oxidative stress, is another factor contributing to hypertension. The cytokine and chemokine release that affect blood pressure regulation can be brought on by inflammation. Oxidative stress can be further exacerbated by inflammatory processes, starting a vicious cycle that leads to persistent hypertension (Chatterjee, 2016).

2.23.5 Oxidative Stress and Antioxidant Defense:

Enzymes like glutathione peroxidase and superoxide dismutase are part of the body's intricate antioxidant defence system (He et al., 2017). Reactive oxygen species are neutralised by these enzymes. Oxidative stress can lead to hypertension when there is an imbalance between the generation of reactive oxygen species (ROS) and antioxidant defences.

2.23.6 Oxidative Stress and Lifestyle Factors:

Blood pressure can be influenced by lifestyle choices such as food, exercise, and exposure to environmental pollutants, which can also affect oxidative stress. Incorporating antioxidant-rich diets, like fruits and vegetables may help reduce oxidative stress and support blood pressure control.

2.23.7 Oxidative Stress and Therapeutic Strategies:

The discovery of the link between oxidative stress and hypertension has prompted the creation of potential therapeutic strategies (Brito et al., 2015; Montezano et al., 2015). Antioxidant therapies and lifestyle changes can help reduce oxidative stress and subsequently lower blood pressure. Oxidative stress and hypertension are closely linked, with oxidative stress contributing to the beginning and development of hypertension. Managing oxidative stress through lifestyle modifications, such eating a healthy, balanced diet, working out frequently, and limiting your exposure to environmental toxins, can help sustain healthy blood pressure levels. Additionally, antioxidant-based therapeutic approaches are being investigated to lessen the chance of associated cardiovascular problems and lessen the impact of oxidative stress on hypertension.

2.24 METABOLIC CHANGES IN PREECLAMPSIA

Preeclampsia is not solely characterized by hypertension and vascular dysfunction; it also involves significant metabolic alterations that impact both the growing foetus and the mother, individuals with preeclampsia have been shown to have changes in their lipid profiles and metabolism (Phalak & Tilak, 2012). These changes impact the health of both the mother and the unborn child, and add to the pathophysiology of preeclampsia.

2.24.1 Lipid profile alterations in preeclampsia.

Women diagnosed in preeclampsia; exhibit notable differences in their lipid levels compared to those experiencing a normal pregnancy (Phalak & Tilak, 2012). During the third trimester,

individuals with preeclampsia demonstrate changes in their serum lipid profile when compared with pregnant women without hypertension (Evrüke et al., 2004; Gohil et al., 2011; Lima et al., 2011). Detecting these variations in lipid markers early, could significantly enhance the management of preeclampsia cases, ultimately improving outcomes for both mother and foetus. The correlation between serum lipid profile and gestational proteinuric hypertension strongly suggests the potential for a novel diagnostic approach. The altered lipid profile also seems to contribute to vascular dysfunction (Zaric et al., 2020) and may influence the development of preeclampsia. Identifying these lipid parameters at an early stage may offer pregnant individuals the opportunity to prevent complications for both mother and foetus, contributing to more effective management of preeclampsia.

2.24.2 Elevated Triglycerides:

Preeclamptic women frequently exhibit increased triglyceride levels (Lima et al., 2011; Ray et al., 2006), the altered lipid profile may contribute to vascular inflammation and endothelial dysfunction. Triglycerides are the major component of the lipid profile. The presence of hypertriglyceridemia is indicative of disturbed lipid metabolism in preeclampsia.

2.24.3 Decreased High-Density Lipoprotein (HDL):

High-density lipoprotein (HDL) cholesterol, often referred to as "good" cholesterol, is essential for lipid metabolism as it assists in removing excess cholesterol from the bloodstream.

In preeclampsia, HDL cholesterol levels decrease (Belo et al., 2002; Einbinder et al., 2018; Phalak & Tilak, 2012), which can contribute to lipid imbalances and cardiovascular risk. HDL cholesterol, known for its protective cardiovascular effects, tends to decrease in preeclampsia, further exacerbating cardiovascular risk.

2.24.4 Dyslipidaemia:

Preeclamptic women may experience a state of dyslipidaemia, with abnormal lipid ratios (e.g., increased triglyceride-to-HDL ratio) that are associated with cardiovascular risk. Dyslipidemia

refers to an abnormal lipid profile marked by elevated triglycerides and reduced HDL cholesterol levels. This pattern of dyslipidaemia is commonly observed in preeclampsia (Sharami et al., 2012), and contributes to the emergence of vascular dysfunction and hypertension.

2.24.5 The impact of preeclampsia on fasting Lipids:

There is a significant correlation between preeclampsia and the levels of total cholesterol, non-HDL-C, HDL-C, and triglycerides measured during pregnancy (Stadler et al., 2023; Timalsina et al., 2016). This finding holds clinical importance as standard lipid panels available in typical clinical laboratories can effectively measure maternal lipid levels. Consequently, employing these affordable lipid panels could provide an accessible means to identify pregnant individuals prone to preeclampsia. To fully comprehend how dyslipidaemia and other elements of the metabolic syndrome, similar to insulin resistance and obesity, preeclampsia develops as a result of more research is necessary. Understanding these correlations might offer insights into potential interventions to manage this association.

2.24.6 Placental lipid transport:

Dysfunctional placental lipid transport mechanisms can result in altered maternal lipid metabolism, influencing fasting lipid levels. The placenta is vital for regulating lipid transfer during pregnancy between the growing foetus and the mother. Lipids are crucial for foetus growth and development, and disruptions in this process can affect both normal pregnancies and complications like preeclampsia. Investigating placental lipid transport in normal pregnancies and its alterations in preeclampsia will greatly improve our knowledge of the preeclampsia pathogenesis.

2.24.7 Placental Lipid Transport in Normal Pregnancy:

In a healthy, normal pregnancy, the placenta enables the transport of lipids from the bloodstream of the mother to the growing foetus. This process is crucial for providing energy and fatty acids essential for the foetus's growth and development.

2.24.8 Lipids in Maternal Circulation:

Maternal lipids, including triglycerides and fatty acids, which enter the circulation through dietary intake or the breakdown of fat stores.

2.24.9 Placental Uptake:

Lipids from the maternal circulation are absorbed by the placenta, which contains particular transport proteins, including FATPs (fatty acid transport proteins) (Duttaroy, 2009) and lipoprotein lipase, which plays key roles in lipid uptake and processing.

2.24.10 Processing and Packaging:

Once inside the placenta, maternal lipids are processed and packaged into lipoprotein particles (Duttaroy, 2009). These particles can carry lipids, such as triglycerides and cholesterol, to the foetus side of the placenta.

2.24.11 Foetus Circulation:

Lipoprotein particles, containing maternal lipids, are released into the foetus circulation, where the developing foetus can take up and utilize these lipids for energy, structural components, and brain development.

2.24.12 Altered Placental Lipid Transport in Preeclampsia:

Preeclampsia is a pregnancy-related condition characterized by elevated blood pressure and impairment of various organ systems. However, it is known that preeclampsia can significantly affect the placenta's functionality (Fisher, 2015; Roberts & Escudero, 2012). One of the key disruptions involves the placenta's ability to transport lipids effectively (Hu et al., 2022). This disruption in lipid transport can have significant implications for both maternal

and foetus health, as lipids are crucial for foetus growth and development. Although the precise mechanisms remain unclear, preeclampsia can disrupt placental function, including the transport of lipids (Hu et al., 2022).

2.24.13 Placental Insufficiency:

Placental insufficiency, or insufficient a source of blood flow for the placenta is a common complication of preeclampsia. This reduced blood flow can impair the placenta's efficiency in transporting lipids, potentially leading to changed lipid profiles in the growing foetus as well as the mother.

Such disruptions in placental lipid transport can impact both maternal and foetus health, possibly contributing to foetus growth restriction and metabolic disturbances in the mother. Understanding these changes is important for improving the management and outcomes of preeclampsia and for developing potential interventions to support placental function in complicated pregnancies.

2.24.14 Placental lipid accumulation:

In preeclampsia, abnormal lipid accumulation and disrupted lipid metabolism have been observed within the placenta (Gil-Sánchez et al., 2012; Hu et al., 2022). This condition leads to an excessive buildup of lipids, which interferes with the normal functioning of placental cells. Lipids play a vital role in providing energy and supporting the structural integrity of cell membranes. However, in preeclampsia, the abnormal lipid buildup can cause cellular stress and contribute to placental dysfunction (Hu et al., 2022; Khaire et al., 2021). The disrupted lipid metabolism also affects the transport of essential fatty acids and other nutrients from the mother to the fetus, potentially impacting foetal growth and development. Understanding these lipid-related abnormalities in the placenta is crucial for developing targeted interventions to mitigate the adverse effects of preeclampsia on both maternal and foetal health.

2.24.15 Implications for Foetus Health:

The availability of vital minerals and essential fatty acids required for the developing foetus may be impacted by maternal lipid alterations in preeclampsia, which may have an effect on foetal growth and development (Gil-Sánchez et al., 2012). Maternal lipid alterations in preeclampsia may influence the availability of minerals and critical fatty acids that the growing foetus needs, potentially impacting foetus growth and development.

Understanding these metabolic changes is essential for managing and mitigating the adverse effects of preeclampsia. Moreover, it emphasizes the importance of a comprehensive method of treatment that attends to the hypertension and metabolic aspects of this complex pregnancy disorder. Future research into the mechanisms underlying these metabolic alterations may pave the way for targeted interventions and improved maternal-foetus outcomes in preeclampsia.

2.25 Liver and Renal Function in Normal Pregnancy.

In preeclampsia, liver and renal functions exhibit distinctive differences compared to a normal pregnancy. These differences can help with the condition's diagnosis and treatment. Liver enzyme abnormalities, such as ALT and AST (aminotransferase) imbalances, might be a signs of preeclampsia (Alese et al., 2021; Mei-Dan et al., 2013; SM et al., 2020). Increased levels of these enzymes may indicate liver damage or impaired liver function, often observed in severe forms of preeclampsia, known as HELLP syndrome. Preeclampsia can lead to increased serum bilirubin levels (August & Sibai, 2017; Breslin et al., 2013), particularly in cases associated with HELLP syndrome. Elevated bilirubin levels may point toward liver dysfunction and potential complications. One of the hallmark features of preeclampsia is proteinuria (Dong et al., 2017; Stillman & Karumanchi, 2007), the presence of excessive protein in urine. This is a defining factor in diagnosing preeclampsia and distinguishes it from a normal pregnancy. Proteinuria is a consequence of impaired renal function and increased glomerular permeability (Stillman &

Karumanchi, 2007). In furthering the complication of Preeclampsia, there are almost always increased levels of serum creatinine (Gupte & Wagh, 2014). While the changes might not be as pronounced in mild cases, severe preeclampsia or eclampsia can lead to elevated serum creatinine levels, indicating compromised kidney function.

A reduction in GFR might be observed in preeclampsia (Conrad et al., 2015; Krutzen et al., 1992), particularly in severe cases. This decrease in GFR indicates impaired kidney function and reduced filtration capabilities. Moreover, preeclampsia is associated with decreased renal blood flow (Conrad & Davison, 2014). This decline can worsen kidney function and aggravate preeclampsia-related complications. Renal and liver function parameters in preeclampsia often contrast sharply with those in a normal pregnancy, where liver enzymes and bilirubin levels usually stay within normal limits (Bacq et al., 1996; Girling et al., 1997). Proteinuria is generally absent in a normal pregnancy or is within negligible limits.

Serum creatinine levels and GFR usually stay consistent or might show slight variations within the normal range during a healthy pregnancy (Larsson et al., 2008). Renal blood flow remains relatively stable without significant reductions observed in preeclampsia.

Understanding these differences in liver and renal function between preeclampsia and normal pregnancy is essential for accurately identifying, tracking, and treating the illness. In severe cases, liver and kidney complications can pose substantial dangers to the foetus and the mother. Renal and hepatic function should be regularly monitored to identify and address potential complications associated with preeclampsia.

2.26 Liver and Renal Function in Preeclampsia

Preeclampsia is characterized by multi-organ involvement, of which there is the need to explore the impact of the condition on renal and liver function, focusing on assessment methods, and the implications for overall organ health.

2.26.1. Renal function assessment in preeclampsia.

Preeclampsia is characterised by renal impairment, and assessing renal function is essential for patient management. Proteinuria and declining kidney function stand as typical indicators of preeclampsia. The kidney, relying on glomerular blood flow and barrier integrity, offers a distinct perspective to comprehend how preeclampsia develops. This overview focuses on the unique anatomical modifications to the kidneys that are seen in preeclampsia and explores the disrupted renal dynamics and factors affecting ultrafiltration. Renal blood flow and glomerular filtration rate (GFR) both decrease in preeclampsia, their absolute levels may still be higher than those in non-pregnant individuals. Key aspects of renal function assessment include:

Serum Creatinine: Elevated serum creatinine levels are indicative of impaired renal function. A significant increase in creatinine levels could be a sign of acute renal injury, a dangerous side effect of preeclampsia.

Glomerular Filtration Rate (GFR): GFR is a more accurate indicator of renal function. A reduced GFR, which is frequently calculated using the MDRD (Modification of Diet in Renal Disease) formula (O'Meara et al., 2006), suggests compromised kidney function.

Urinary Protein Excretion: Quantifying urinary protein excretion is essential for diagnosing and monitoring preeclampsia. A 24-hour urine collection or a protein-to-creatinine ratio can be used to diagnose proteinuria.

Blood Urea Nitrogen (BUN): Increased BUN levels can signal impaired kidney function, although it is less specific than creatinine or GFR.

Reduced Glomerular Filtration Rate (GFR): Preeclampsia can reduce the glomerular filtration rate, pointing to a decreased kidney's capacity to remove waste and extra material from the circulation. A reduced GFR can lead to waste product accumulation in the bloodstream.

Endothelial Dysfunction: Endothelial dysfunction, characteristic of preeclampsia, can also impact the renal vasculature. This can contribute to vasoconstriction, reducing blood flow to the kidneys and further impairing their function.

Renal Ischaemia: Reduced renal blood flow as a result of inadequate placental remodeling can lead to renal ischaemia, causing damage to renal tissue.

Renal Microthrombi: Microclots or thrombi can form in the renal blood vessels in severe cases of preeclampsia, further compromising renal function.

2.26.2 Liver function assessment in preeclampsia.

Liver involvement in preeclampsia (Alese et al., 2021; Chandrasekaran & Simon, 2020; Hammoud & Ibdah, 2014) can lead to significant morbidity. Evaluation of liver function is essential for managing and detecting hepatic problems early on.

Important elements in evaluating liver function consist of:

Liver Enzymes: Alanine transaminase (ALT) and Aspartate transaminase (AST) are two liver enzymes that can identify hepatic dysfunction. Elevated levels may indicate liver injury.

Bilirubin: Elevated bilirubin levels, particularly direct (conjugated) bilirubin, may indicate impaired liver function.

Lactate Dehydrogenase (LDH): LDH serves as an indicator of tissue damage and is frequently elevated in preeclampsia, indicating liver involvement.

Coagulation Profile:

Hepatic dysfunction may be suggested by abnormalities in blood coagulation tests (Amitrano et al., 2002; Marks, 2013). For instance, a prolonged activated partial thromboplastin time (aPTT) or prothrombin time (PT) indicates potential issues with the liver's ability to produce clotting factors (Marks, 2013). These coagulation tests measure the time it takes for blood to clot, and extended times can signal liver impairment, as the liver is crucial for synthesizing many of the proteins involved in the coagulation process. Therefore, when these times are prolonged, it often

points to a dysfunction in hepatic function, potentially due to liver disease or damage, which affects its ability to maintain normal blood clotting mechanisms.

2.26.3 Pathophysiology of liver disease in preeclampsia:

Preeclampsia can also affect the liver (Hammoud & Ibdah, 2014), leading to hepatic dysfunction. The liver is responsible for various vital functions, including metabolizing nutrients, detoxifying the bloodstream, and producing important proteins. Liver function can be impacted by preeclampsia in:

Hepatic Ischaemia: Similar to the kidneys, the liver can experience reduced blood flow due to placental insufficiency and systemic vasoconstriction. This can result in hepatic ischaemia, contributing to liver damage.

Elevated Liver Enzymes: Liver damage in preeclampsia may manifest as elevated levels of liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which signify hepatic stress or injury (Eastabrook et al., 2011).

HELLP Syndrome: Severe preeclampsia may give rise to a condition called HELLP syndrome. Significant liver damage, low platelet counts, elevated liver enzymes, and haemolysis (the disintegration of red blood cells), are all features of this illness.

Impaired Coagulation: Liver dysfunction can impair the production of blood clotting factors and proteins involved in coagulation, raising the risk of bleeding complications.

Both renal and liver dysfunction in preeclampsia can result in complications such as edema, organ damage, elevated blood pressure, and, in severe cases, multi-organ failure (Eastabrook et al., 2011). Timely diagnosis and effective management are vital for reducing the impact of these dysfunctions. Regular prenatal care and close monitoring by healthcare providers are essential for identifying and managing these issues in pregnant individuals with preeclampsia.

2.26.4 Implications for organ health in preeclampsia.

Preeclampsia is a pregnancy-related hypertension disease that causes multiple organ failure, primarily affecting the placenta in the latter stages of pregnancy. It stands as a major contributor to maternal health complications, necessitating intensive care admissions, increasing the likelihood of Caesarean section, causing damage to vital organs, and posing risks for foetus complications.

The impact of preeclampsia on renal and liver function extends beyond the immediate perinatal period:

Long-term Implications: Preeclampsia-associated renal and hepatic dysfunction may have long-term health implications for affected women. Chronic kidney disease may be more likely to develop in those with kidney impairment, and hepatic problems may also lead to lasting liver dysfunction.

Maternal Morbidity: Severe renal or hepatic involvement can result in maternal morbidity, including acute kidney injury, hepatic haematoma, or hepatic rupture.

Foetus Implications: Impaired maternal organ function can also affect foetus well-being, emphasizing the need for close monitoring and timely interventions.

Recurrence Risk: A woman who experiences hepatic problems during one pregnancy may be more likely to experience similar problems during subsequent pregnancies. Comprehensive assessment of renal and liver function in preeclampsia is crucial for guiding clinical management, risk stratification, and guaranteeing the mother's and the foetus's health and well-being. Improved results and suitable therapies are made possible by early diagnosis of organ dysfunction.

2.27 BIOCHEMISTRY PROFILES IN PLACENTAL AND VENOUS BLOOD IN PREGNANCY

In preeclampsia, the chemical composition of both venous and placental blood exhibits distinct differences when compared to that of a typical pregnancy (Kharb & Nanda, 2017), these variations can include altered levels of key biochemicals and metabolites. For instance, in preeclampsia, there may be elevated levels of uric acid, liver enzymes (such as AST and ALT), and markers of oxidative stress in the maternal venous blood. Additionally, placental blood in preeclamptic pregnancies often shows higher concentrations of inflammatory cytokines and abnormal lipid profiles (Conrad & Benyo, 1997; Huang et al., 2013).

These chemical patterns are indicative of the systemic inflammation and endothelial dysfunction that are characteristic of preeclampsia. The elevated levels of oxidative stress markers suggest increased cellular damage, while the altered lipid profiles can affect the placental function and the nutrient supply to the foetus. Preeclamptic women also have elevated levels of TSH and haemoglobin oxygenase 1 (Kharb & Nanda, 2017).

The aetiology and diagnostics of preeclampsia are aided by these variations. Elevated levels of markers linked to placental malfunction are often seen in placental blood in preeclampsia (Benton et al., 2016). Among these are soluble endoglin (sEng) and soluble fms-like tyrosine kinase 1 (sFlt-1), which are connected to endothelial dysfunction and the onset of preeclampsia. The defining feature of this disease is an imbalance in angiogenic factors. Anti-angiogenic factors like sFlt-1 and sEng, which oppose pro-angiogenic factors like VEGF and PlGF, are more concentrated in placental blood (Jardim et al., 2015). This mismatch has a role in vascular remodelling impairment, hypertension, and endothelial dysfunction. Elevated blood pressure and other hypertensive markers are frequently seen in venous blood in preeclampsia (Qu & Khalil, 2020), It sets it apart from an ordinary pregnancy. Systemic inflammation and endothelial dysfunction may be connected to these alterations, which exacerbates the hypertensive symptoms of preeclampsia. Preeclamptic women's venous blood biochemistry

profiles may show anomalies in markers linked to liver and renal function. Changes in creatinine levels and elevated liver enzymes (ALT, AST) may be signs of renal and hepatic disease. (Ekun et al., 2018; Khan et al., 2023), especially in severe instances connected to HELLP syndrome.

In a normal pregnancy, placental blood typically maintains a balance between anti-angiogenic and angiogenic factors without significant disruptions observed as in preeclampsia (Umapathy et al., 2020). Venous blood parameters, including liver and renal function markers, usually remain within the normal range in a healthy pregnancy, contrasting the alterations seen in preeclampsia. Monitoring biochemistry profiles in both placental and venous blood is pivotal in diagnosing and managing preeclampsia. The identification of specific markers associated with placental dysfunction, endothelial damage, and abnormal angiogenesis in placental blood, alongside markers of systemic inflammation and organ dysfunction in venous blood, aids in diagnosing the condition and predicting its severity. Assessing specific markers like superoxide anion, hydrogen peroxide, and hydroxyl radicals, could indicate increased or decreased oxidative stress levels. F2-isoprostanes and malondialdehyde (MDA), sometimes referred to as 4-hydroxynonenal (4-HNE), are measured to detect lipid peroxidation and oxidative damage to lipids. Furthermore, the levels of enzymes such as glutathione reductase (GR), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) can be used to evaluate the activity of the blood's antioxidant defence system. Likewise, reactive oxygen species indicators have been found in placental homogenate, suggesting that localised oxidative stress occurs within the placental tissue. Lipid peroxidation products, including 4-HNE or MDA, are indicators of oxidative damage to lipids in placental tissue when they are found in placental homogenate. Moreover, the placental homogenate's levels of antioxidant enzymes as SOD, CAT, GPx, and GR show the local antioxidant defence mechanisms against oxidative stress.

Comparing these markers between blood and placental homogenate provides a comprehensive understanding of systemic and local oxidative stress levels in preeclampsia. Elevated levels in both compartments suggest a widespread impact of oxidative stress on maternal circulation and placental tissue, contributing to the pathophysiology of preeclampsia. These distinct biochemistry differences between preeclampsia and normal pregnancy enable clinicians to identify high-risk pregnancies earlier and implement appropriate management strategies to reduce difficulties for the foetus and the mother. Moreover, there exists information on malaria parasite sequestration in the placental tissues and their concomitance relationship with oxidation stress among preeclamptic women. Sequestration of malaria parasites in placental tissue is associated with unfavourable outcomes for the foetus and mother (Chua et al., 2021; Kapisi et al., 2017). Regular monitoring of these biochemistry parameters and malaria parasites is crucial in managing and preventing adverse outcomes associated with preeclampsia.

2.28 PLACENTAL MALARIA IN NORMAL AND PREECLAMPSIA PREGNANCY.

Placental malaria is a disorder that affects pregnant women when the malaria parasite penetrates the placenta. It is directly linked to adverse outcomes for both the mother and the baby. (Chua et al., 2021; Kapisi et al., 2017). Its link to conditions like preeclampsia and its comparison with normal pregnancies sheds light on the complexities of pregnancy-related complications. Placental malaria substantially increases the chance of developing preeclampsia (Zakama et al., 2020). Preeclampsia may arise as a result of immunological responses triggered by the interplay between malaria infection and the placenta (Sharma & Shukla, 2017). This infection can lead to placental damage, impairing its function and potentially causing complications like hypertension, proteinuria, and organ dysfunction characteristic of preeclampsia. In contrast to preeclampsia, where the association is stronger, Placental malaria can still have adverse effects on a healthy pregnancy (Kapisi et al., 2017; Singh et al., 2014; Uneke, 2007), albeit to a lesser

extent. The infection may hinder the placenta's capacity to deliver nutrients and oxygen to the foetus even in the absence of hypertensive conditions. This may lead to low birth weight, premature delivery, and intrauterine growth restriction (IUGR) (Christensen et al., 2011; Kidima, 2015; Matteelli et al., 1997; Umbers et al., 2011). The inflammatory response that placental malaria causes the placenta to accumulate immune cells and pro-inflammatory cytokines. The placenta's ability to support the developing foetus is compromised by this inflammation, which alters its structure and function (Gaccioli & Lager, 2016). Furthermore, the placenta's retention of contaminated red blood cells worsens tissue damage and reduces blood flow (Costa et al., 2020).

Diagnosing placental malaria involves examining placental tissue for the presence of malaria parasites and related histopathological changes. Antenatal screening and appropriate treatment of malaria during pregnancy are crucial in endemic regions to mitigate its impact on both maternal and foetus health. Managing placental malaria in the context of preeclampsia requires a multifaceted approach. It involves not only addressing the hypertensive disorder but also managing the underlying malaria infection. Treatment strategies often involve antimalarial drugs to clear the infection and specific interventions to manage preeclampsia's complications.

Continued research aims to elucidate the intricate mechanisms linking placental malaria with preeclampsia and its impact on normal pregnancies.

Comprehending these correlations can facilitate the creation of focused interventions and proactive action in preventing adverse birth outcome in pregnancies.

To lessen the burden of difficulties related to placental malaria, options for efficient antimalarial prophylaxis and treatment during pregnancy continue to be a focus.

The development of preeclampsia and the risks to normal pregnancies are significantly impacted by the presence of placental malaria, which impairs placental function. Further investigation into

its pathophysiology and its implications for maternal and foetus health is crucial for improved diagnostic and therapeutic strategies in affected populations.

2.29 PREDICTIVE ACCURACY OF PLACENTAL AND SERUM BIOCHEMISTRY MARKERS FOR PREECLAMPSIA.

Preeclampsia is a complicated hypertensive pregnancy illness, presents a significant challenge for early diagnosis and management. Identifying reliable predictive markers is crucial for timely intervention and improved outcomes. Placenta and serum Biochemistry markers offer clinicians useful tools for potentially predicting when preeclampsia begins and how severe it is.

2.29.1 Placental biochemistry markers

Placental Growth Factor (PlGF):

The development of new blood vessels and angiogenesis depend on the placental growth factor, or PlGF. PlGF levels are typically lowered in preeclampsia. Low PlGF levels in the early phases of pregnancy have been linked to a higher chance of preeclampsia, according to research. making it a useful marker for early identification and risk stratification (Creswell et al., 2023). The predictive accuracy of PlGF is enhanced when combined with other markers or clinical parameters, guiding the timing and frequency of antenatal visits (Velegrakis et al., 2023).

Soluble fms-like Tyrosine Kinase-1 (sFlt-1):

Soluble fms-like tyrosine kinase-1 (sFlt-1) is an anti-angiogenic factor that counteracts the effects of PlGF and VEGF. Increased sFlt-1 levels may indicate preeclampsia. Elevated sFlt-1 levels, especially in the second and third trimesters, strongly predict preeclampsia (Ohkuchi et al., 2014). As a prognostic metric, the sFlt-1/PlGF ratio works especially well (Birdir et al., 2018). Monitoring sFlt-1 levels can aid in early identification and management, allowing for closer surveillance and timely intervention (Poon et al., 2020).

2.29.2 Serum biochemistry markers

Uric Acid:

Preeclampsia is frequently accompanied by increased uric acid, a result of purine metabolism. Early in pregnancy, elevated uric acid levels may indicate a higher risk of preeclampsia. But as a stand-alone marker, its sensitivity and specificity are constrained (Corominas et al., 2022a). While not highly specific, elevated uric acid levels can prompt closer monitoring and consideration of additional predictive tests (Corominas et al., 2022a).

Pregnancy-Associated Plasma Protein-A (PAPP-A):

The glycoprotein known as pregnancy-associated plasma protein-A, or PAPP-A, is secreted by the placenta and is often tested during the first trimester of pregnancy. Preeclampsia and other unfavourable pregnancy outcomes have been associated with low PAPP-A levels early in pregnancy (Kalousova et al., 2014; Ranta et al., 2011; Spencer et al., 2008). Women at risk for preeclampsia can be identified with the use of PAPP-A levels as part of first-trimester screening (Kalousova et al., 2014).

2.29.3 Combined marker approaches:

sFlt-1/PlGF Ratio

One accurate way to diagnose preeclampsia is to look at the ratio of sFlt-1 to PlGF. An angiogenic factor imbalance, which is common in preeclampsia, is indicated by a high sFlt-1/PlGF ratio (Velegrakis et al., 2023). This ratio has demonstrated exceptional sensitivity and specificity in predicting the onset of preeclampsia, particularly in the second and third trimesters (Poon et al., 2020). It can be used to evaluate the severity and expected course of the illness, as well as to confirm the diagnosis of preeclampsia (Creswell et al., 2023; Velegrakis et al., 2023).

2.29.4 Other marker combinations:

Combining many markers, including PlGF, sFlt-1, and PAPP-A, and uric acid, along with maternal risk factors and ultrasound findings, can enhance predictive accuracy. Combining

markers improves sensitivity and specificity, providing a more comprehensive assessment of preeclampsia risk (Yusuf et al., 2018). These combined approaches can guide clinical decision-making, allowing for personalized monitoring and management plans (Velegrakis et al., 2023).

2.29.5 Research and Future Directions:

Ongoing research aims to refine predictive models and identify additional markers that could improve the early detection of preeclampsia. Advances in proteomics and genomics may uncover novel biomarkers, enhancing predictive accuracy and enabling more precise risk stratification (Myers et al., 2013; Nguyen et al., 2019).

2.29.6 Conclusion:

Biochemistry markers seen in the serum and placenta, including PAPP-A, sFlt-1, uric acid, and PlGF, are important indicators of preeclampsia. While individual markers provide valuable insights, combined marker approaches offer the best predictive accuracy. Incorporating these markers into routine prenatal care can facilitate early identification, closer monitoring, and timely intervention, enhancing the outcomes of preeclamptic pregnancies for both the mother and the baby.

2.30 CURRENT RESEARCH GAPS IN PREECLAMPSIA

Preeclampsia remains a challenging and complex pregnancy-related disorder, and continuous research is vital to advance our understanding the treatment of the illness.

Preeclampsia still has alot of unanswered research questions, and filling them could have a significant effect on the mother's and the foetus' health.

There are currently gaps in the following studies on preeclampsia:

Aetiology and Pathogenesis: Even though our knowledge of the pathophysiology of preeclampsia has greatly increased, the exact reason of the condition is still unknown.

Researchers continue to investigate the precise mechanisms behind placental dysfunction, maternal immune responses, genetic factors, and their involvement in the development of preeclampsia.

Predictive Biomarkers: Identifying reliable predictive biomarkers for preeclampsia remains a major research challenge. Developing accurate and early indicators of preeclampsia risk could improve patient care and potentially lead to preventive interventions.

Risk Stratification: Research is needed to refine risk stratification models that consider a combination of clinical, genetic, and biomarker data. This can help identify high-risk pregnancies early and tailor management strategies accordingly.

Preventive Strategies: Using efficient preventative strategies is necessary to lower the incidence and severity of preeclampsia. Along with medicinal methods, lifestyle modifications like food and exercise are being investigated in ongoing research.

Management Strategies: Optimizing the management of preeclampsia, which includes blood pressure control, anticoagulation, and seizure prophylaxis, is an area of active research. Personalized treatment approaches tailored to the severity of the condition and individual patient characteristics are being explored.

Long-Term Outcomes: It is imperative to conduct research on the enduring health implications of preeclampsia for both mothers and their offerings. Understanding the impact on cardiovascular health, metabolic disorders, and neurodevelopmental outcomes can inform postpartum care and interventions.

Foetus Monitoring: Developing better methods for monitoring foetus well-being in pregnancies complicated by preeclampsia is crucial. This includes lead to investigating novel technologies and strategies for assessing foetus growth, oxygenation, and overall health.

Precision Medicine: Research is ongoing to explore the potential for precision medicine approaches in preeclampsia. Personalizing treatments according to individual patient characteristics and genetic profiles could enhance outcomes.

Global Disparities: Addressing disparities in the incidence and outcomes of preeclampsia among different populations and regions is important. Research should examine the underlying causes of these disparities and identify strategies to reduce them.

Patient-Centred Care: Research on the experiences and preferences of women with preeclampsia can inform patient-centred care models. Comprehending the psychosocial aspects of the condition and its impact on quality of life is crucial.

Translational Research: Closing the gap between basic science and clinical practice is crucial. Translational research can facilitate the development of innovative therapies and interventions for preeclampsia.

Economic Impact: Evaluating the economic impact of preeclampsia on healthcare systems and society needs to be addressed. Cost-effective strategies for prevention, management, and follow-up care should be explored.

Addressing these research gaps requires collaboration among researchers, clinicians, and policymakers. Enhancements in the diagnosis, treatment, and prognosis of preeclampsia can benefit mothers and their infants.

CHAPTER 3
MATERIALS AND METHODS

3.1 STUDY SETTING:

The study was conducted at Bolgatanga, which is located in Ghana's Upper East Region. This area is situated in the northeastern section of the nation, between latitudes 10° 30' N and 11° N and longitudes 0° and 1° West. It borders the Republic of Togo to the east and Burkina Faso to the north internationally (Asuo-Mante et al., 2016). The people in these three countries have many cultural similarities: agricultural methods, transportation of food and produce, language, social customs, and Value systems. There is a significant movement across borders involving people, goods, and services. The difficulties concerning disease monitoring and management, especially in healthcare provision, due to these geographical, social, and cultural ties, are incredibly significant and should not be underestimated. The settlement pattern in the region is highly dispersed across 911 communities. Five main languages are spoken in this area: Kasem, Gurune, Bisa, Kusal, and Builli.

3.2 THE STUDY SITE

The Bolgatanga Regional Hospital is a key provider of health delivery services in the Upper East Region of Ghana. The hospital was established to serve the medical needs of the local population, it has significantly contributed to promoting health and well-being in the area. The health facility provides a comprehensive array of medical services including: Obstetrics and gynaecology, general medicine, surgery, pediatrics, mental health care, ophthalmology, laboratory diagnostics, physiotherapy, radiography, Ear, Nose and Throat (ENT)services, and mortuary services. It is equipped with modern facilities and staffed by highly trained healthcare professionals. Bolgatanga Regional Hospital is well-prepared to handle

emergencies with its dedicated emergency department. The team is trained to respond swiftly to critical situations, providing timely and life-saving interventions.

Recognizing the importance of maternal and child health, the hospital has special units and Programs to support expectant mothers and young children. This includes antenatal care, postnatal care, and vaccination services. The hospital actively engages with the local community through health education programs, outreach initiatives, and preventive healthcare campaigns. This proactive approach aims to improve overall community health and reduce the incidence of preventable diseases. Bolgatanga Regional Hospital leverages modern medical technologies to enhance diagnostic accuracy and treatment outcomes.

This dedication to staying updated with advancements in healthcare guarantees that patients receive optimal care. The Bolgatanga Regional Hospital serves as a beacon of healthcare in the Upper East Region, delivering essential medical services to the community. Through its commitment to quality care, community engagement, and ongoing professional improvement training, the hospital is crucial in improving the health and well-being of the community it serves.

3.3 STUDY DESIGN.

The research was carried out in 2022, from January to December, utilized a case-control design. This retrospective observational approach compares individuals with a specific condition to those without it to identify potential risk factors, making it valuable for studying rare outcomes efficiently. Sociodemographic or anthropometric variables were not matched during the selection process (unmatched). The ratio of cases to controls was 1:1.5. Simple random sampling was employed for the recruitment of study subjects. This involves selecting

participants from the general public in a way that every individual has an equal chance of being chosen. This method of sampling allows equal representation of the population, reduces selection bias as well promotes the feasibility of the study; with the help of software tools for generating random numbers.

3.4.0 STUDY POPULATION

The research focused on expectant mothers admitted to the maternity ward of the Upper East Regional Hospital. The study involved 250 participants: 100 women diagnosed with preeclampsia and 150 pregnant women without the condition, all aged between 18 and 41 years. A practicing Obstetrician and Gynaecologist diagnosed preeclampsia based on criteria typically identified after 20 weeks of gestation:

1. **Blood Pressure**:
    - Systolic blood pressure of 140 mm Hg or higher, or diastolic blood pressure of 90 mm Hg or higher, measured on two occasions at least four (4) hours apart in a previously normotensive woman.
2. **Proteinuria**:
    - A 24-hour urine collection containing 300 mg or more of protein (or an equivalent amount estimated from a timed collection).
    - A protein to creatinine ratio of at least 0.3.
    - A 1+ dipstick reading is only utilised in the absence of additional quantitative techniques.

Or, in the absence of proteinuria, new-onset hypertension with the following severe features:

3. **Thrombocytopenia**:
    - Platelet count below 100,000/µL.
4. **Renal Insufficiency**
    - A serum creatinine concentration of more than 1.1 mg/dL, or two times that amount when no other renal disorders are present.
5. **Liver Involvement**:
    - Blood concentrations of liver transaminases that are twice the normal level.
6. **Pulmonary Edema**:
    - Presence of pulmonary edema.
7. **Cerebral or Visual Symptoms**:
    - New-onset headache that remains unresponsive to medication and cannot be attributed to other diagnoses, or visual disturbances such as photopsia, scotomata, cortical blindness, or retinal vasospasm.
    - These criteria support the prompt and accurate diagnosis of preeclampsia, allowing for effective management and intervention at both the Antenatal Clinic and the gynaecology ward of the Upper East Regional Bolgatanga, Ghana.

3.4.1 Inclusion Criteria;

Preeclampsia is characterized by the abrupt onset of sustained systolic blood pressure exceeding 140 mmHg, diastolic blood pressure above 90 mmHg, and persistent proteinuria (300 mg protein/24 hours) after the 20th week of pregnancy, excluding urinary tract infections (Reddy et al., 2021; Tanner et al., 2022). The study comprised these women. The number of foetuses lost after 22 weeks of pregnancy plus the number of newborn fatalities within the first 28 days, divided by 1,000 births, is known as the perinatal mortality rate (MacDorman & Kirmeyer, 2009; Organization, 2006a). Gestational age was determined using either the last menstrual period or an early ultrasound conducted in the first or early second trimester. The women were classified based on definitions from the National Heart, Lung, and Blood Institute (Pemberton et al., 2010) and the WHO (De Onis, 2015; López Stewart, 2014; Wendland et al., 2012) divided into four groups: Lean (BMI < 20.0 kg/m²), Normal (BMI = 20.0–24.9 kg/m²), Overweight (BMI = 25.0–29.9 kg/m²), and Obese (BMI ≥ 30 kg/m²). Pregnancy outcome variables assessed included low birth weight (< 2500 g), foetus macrosomia (≥ 4000 g), small for gestational age (below the sex-specific 10th percentile), preterm delivery (< 37 weeks gestation), very preterm delivery (≤ 32 weeks gestation), Caesarean delivery, maternal death, and infant death within the first year (Miller Jr, 1988; Williams & Chen, 1982). The study enrolled women who were previously diagnosed with preeclampsia during their second and third trimesters, as well as healthy pregnant women without preeclampsia (uncomplicated pregnancies), provided they consented to participate, and were included as controls.

3.4.2 Exclusion Criteria;

Women with endocrinopathy and a history of inflammatory conditions like rheumatoid arthritis and systemic lupus erythematosus (SLE), as well as multiple pregnancies, were criteria for exclusion from the study. Additionally, pregnant women with chorioamnionitis, villitis of unknown etiology (VUE), or those undergoing corticosteroid treatment for inflammatory conditions were also excluded from the study.

3.4.3 Sample Size Determination

The mode of delivery as an outcome variable was considered in calculating the sample size. According to a prior study in Ghanaian, only 14.89% of pregnant women without preeclampsia had a Caesarean section, compared to 65.79% of women with preeclampsia (Ahenkorah et al., 2022). The following assumptions were made using the Kelsey (Charan & Biswas, 2013) formula in Epi Info (v7) (:https://www.cdc.gov/epiinfo/pc.html)

$$\text{Sample size} = \frac{r+1}{r}\frac{(p^*)(1-p^*)(Z_\beta + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

r = Ratio of control to cases which is 2.0

p* = Average proportion exposed = proportion of exposed cases + proportion of control exposed/2

Z_β = Standard normal variate for power = 80%

Za/2 = Standard normal variate for the level of significance as mentioned in the previous section.

p1 – p2 = Effect size or difference in proportion expected

The margin of error=5% (95% confidence interval)

From the analysis, the minimum sample size = 65 (cases=22 and controls=43)

3.5.0 DATA COLLECTION AND MEASUREMENTS.

A validated semi-structured questionnaire was employed to collect sociodemographic, obstetric, and clinical information from the pregnant women. Data on the newborns, including birth weight and placenta weight, were also gathered. The data was gathered through interviews and by examining the women's medical records. Utilizing a semi-structured questionnaire for maternal and foetus data collection involves a combination of predefined questions and open-ended prompts. This method ensures the collection of essential information while allowing respondents to offer detailed, personalized responses. The questionnaire has been designed to include specific questions about demographic information (age, socioeconomic status), medical history, pregnancy details, and foetus health indicators, as well as Open-Ended Questions to explore experiences, perceptions, and additional details about pregnancy, childbirth, and foetus outcomes.

The study ensures interviewers understand the objectives of the study and are familiar with the questionnaire. Interviewers (Nurses) were trained in interviewing techniques, particularly on how to handle open-ended questions and probe for further information without leading the respondent. Their training also included how to administer consent forms and information sheets explaining the study's purpose, procedures, and confidentiality assurances.

Open-ended questions such as "Could you describe any challenges you faced during your prenatal visits?", "How did you feel about the information and support provided by your

healthcare provider?" "Can you share more about any complications you experienced during your pregnancy?"

Probing and Clarifying questions to elicit more detailed responses, such as "Can you tell me more about that?" or "How did that make you feel?", all information was recorded accurately, ensuring that both structured answers and detailed open-ended responses were captured. All questionnaires were reviewed for completeness and clarity immediately after the interview.

The data were inputted into an Excel sheet for analysis, ensuring accuracy and consistency.

Predefined questions such as demographics: What is your age? Which degree is the highest you have earned? How many times have you given birth?

do you have a history of hypertension? how many weeks pregnant are you?

have you experienced any symptoms of preeclampsia (e.g., high blood pressure, swelling)? Have you had any ultrasounds? what were the results? how often do you feel your baby move? Were all asked and recorded. Obstetric data collected included a comprehensive information related to pregnancy, childbirth, and postpartum period which was collect as follow: maternal age, Parity (number of previous pregnancies), Gravidity (total number of pregnancies, including current), Socioeconomic status, Pre-existing health issues (such as diabetes, hypertension), a family history of pregnancy-related problems (such as gestational diabetes, preeclampsia), Previous obstetric history (e.g., miscarriages, stillbirths, preterm births), gestational age, Blood pressure readings, Presence of edema, Symptoms of preeclampsia (e.g., headaches, visual disturbances, upper right abdominal pain), Symptoms of gestational diabetes (e.g., excessive thirst, frequent urination), Rh factor and blood type,

Results of routine blood tests (e.g., haemoglobin levels, liver function tests), Urinalysis results (e.g., proteinuria), Date and time of labour onset, Type of labour (spontaneous, induced, augmented), Duration of labour (first, second, and third stages), Mode of delivery (vaginal or Caesarean section), reasons for Caesarean section if applicable, complications during labour and delivery (e.g., foetus distress, shoulder dystocia, postpartum haemorrhage), Apgar scores at 1 and 5 minutes, newborn birth weight and length, and placental weight and appearance.

3.5.1 Blood Pressure Measurement;

We took blood pressure readings between 7:00 and 10:00 in the morning local time. After a 15-minute break, the ladies were seated and a skilled midwife used a standard mercury sphygmomanometer to take their measurements twice. By timing the onset of the first Korotkoff sound and the end of the fifth, blood pressure was measured. High DBP (90 mmHg) and high SBP (140 mmHg) were the criteria for high blood pressure and high systolic blood pressure, respectively (Chobanian, 2017; Chobanian et al., 2003).

3.5.2 Anthropometric Measurements;

An electrical weighing scale (Seca Alpha, GmbH & CO, Igni, France) was used to measure the subject's body weight with an accuracy of 0.5 kg. On the scale, participants stood motionless while dressed comfortably and without shoes. The Ghana Standards Authority's known weights were used to calibrate the scale, which has a precision of 100 g and a range of 0.1-150 kg. Participants were asked to stand erect against a vertical scale in the Frankfurt plane posture while a portable stadiometer (Pfifter, Carlstadt, NJ, USA) was used to measure standing height accurately to the nearest 0.1 centimeter. The stadiometer has an accuracy of 1 mm and a range of 70-205 cm. According to the World Health Organization's 2009

recommendation, body weight in kilograms divided by height in meters squared was used to compute body mass index (BMI) (De Onis, 2015).

3.5.3 Determination of Placental Weight and Shape

An electronic balance was used to determine each placenta's weight (Camry 206; 0.0-120 kg) and recorded along with its pathological number. Each placenta was examined for any lesions, and its shape was described as either irregular, oval, round, or succenturiate lobes while that of the umbilical cord was measured and observed for the presence of a true knot and also described based on its insertion; central, paracentral, eccentric, marginal and velamentous. The colour of the umbilical cord was described as; clear, semi-opaque, and opaque.

3.6.0 BLOOD AND PLACENTAL TISSUE COLLECTION.

Following childbirth, 5 millilitre's sample of venous blood was collected from the antecubital vein, whilst placenta's cotyledon was removed with scissors. 3 millilitres of blood samples were placed in serum separator tubes for biochemistry analysis, and the remaining 2 millilitres were dispensed into EDTA vacutainer tubes for a full blood count analysis. 1ml of maternal intervillous blood was collected into a heparinized sample bottle and a placental smear made, using the pool-biopsy technique (Daud et al., 2022; Walker-Abbey et al., 2005) for parasitological studies. The colour of the placenta and the cord insertion were examined, followed by weighing the infants and placentas using a Seca weighing scale. The length of the umbilical cord was measured using a non-stretchable tape measure. After clotting, the blood in the gel-separator tubes was spun in a centrifuge at 8000 rpm for about 5 minutes to yield serum which was immediately frozen at -80°C as well as placenta tissues before analysis at a convenient time. Weighing the infants and placentas with a Seca weighing scale

after examining the colour of the placenta and the cord insertion. A non-stretchable tape measure was used to measure the umbilical cord's length. und

3.6.1 Haematological Analysis:

The whole venous blood samples in EDTA Vacutainers tubes were mixed well by gentle rotation before being run on the 5-part Sysmex Haematology analyzer for complete blood count.

3.6.2 Tissue Homogenization:

Within an hour post-delivery, approximately 25 to 60g fragments (equivalent to 1-2 cotyledons) of placental tissue were sliced from the villous tree of each placenta. These slices underwent thorough rinsing with phosphate buffer saline (PBS) to eliminate excess blood and were then either stored at −80 °C or homogenized in ice-cold phosphate buffer saline (consisting of KCl 140 mmol/L, phosphate 20 mmol/L, pH 7.4) at a ratio of about 0.5g tissue per 1 ml. The homogenates were subsequently centrifuged for 15 minutes at -20^{o}C at 5000 x g, following which the supernatant was withdrawn and promptly analyzed or portioned and stored at -80°C within the Navrongo Health Research Centre.

3.6.3 Peripheral and Placental Malaria Microscopy:

A more reliable indicator of malaria infection during pregnancy is the examination of placental blood films for malaria parasites after deliveries (Gupta et al., 2001; Mishra & Misra, 2007)**.** Two microscopists evaluated thin and thick peripheral and placental blood smears stained with a Giemsa solution. A slide was deemed negative only after at least 200 fields were examined for malaria parasites. If parasites were found in the mother's placenta or peripheral blood and counted, the mother was considered malaria-positive.

A third microscopist settled any inconsistent positives in circumstances where the data were contradictory (Swysen et al., 2011).

3.6.4 Examination and Quantification

Examination:

Before the examination, an immersion oil drop was applied to the stained smears, followed by examining the smears under a microscope using a 100x oil immersion lens.

The Thick Smear Examination procedure was as follows:

Detection: Scan the thick smear to detect the presence of malarial parasites.

Counting: A count of 200 white blood cells (WBCs) indicates the quantity of parasites. In the event of a high parasite density, count using 100 WBCs.

Record the number of parasites observed.

The Thin Smear Examination procedure was as follows:

Species Identification: Examine the thin smear to identify the species of Plasmodium based on the morphology of the parasites and the infected red blood cells (RBCs).

Quantification:

Thick Smear Quantification: Calculation of the parasite density was done using the formula:

$$\text{Parasites per microliter} = \left(\frac{\text{Number of parasites counted}}{\text{Number of WBCs counted}} \right) \boxed{\text{X Patient's WBC count}}$$

Assume a standard WBC count of 8000 cells/µL if the patient's WBC count is not available

$$\text{Parasites per microliter} = \left(\frac{\text{Number of parasites counted}}{200} \right) \boxed{\text{X 8000}}$$

Thin Smear Quantification (if needed):

Count the number of infected RBCs in a specified number of total RBCs (e.g., per 1000 RBCs), and calculation of the parasitemia percentage was done as shown below:

Thin Smear Quantification (if needed):

- Count the number of infected RBCs in a specified number of total RBCs (e.g., per 1000 RBCs) and calculate the parasitaemia percentage:

$$\text{Parasitemia (\%)} = \left(\frac{\text{Number of infected RBCs}}{\text{Total Number of RBCs Counted}} \right) \boxed{\text{X 100}}$$

Reporting Results:

Positive Result: Results were reported of the presence of malarial parasites, the species identified, and the parasite density (parasites/µL).

Negative Result: Results were reported of the absence of malarial parasites after examining at least 100 fields in the thick smear.

3.7.0 BIOCHEMISTRY ANALYSIS.

3.7.1 Placenta Homogenate Biochemistry Analysis:

Triglycerides, total cholesterol, high-density lipoprotein cholesterol, uric acid, urea, creatinine, glucose, ALT, and AST were measured from the supernatants obtained from both the placental homogenates and blood samples. The BT 5000® Random Access Chemistry Analyser from Biotecnica, Italy, was used for this study, and the manufacturer's instructions were followed. Envoy® 500 reagents were obtained from Vital Diagnostics, USA.

3.7.2 Placenta Homogenate Malondialdehyde (MDA):

We used the techniques outlined by Kamal et al. (1989) and Shlafer and Shepard (1984) to determine the levels of oxidative stress. The assay known as thiobarbituric acid (TBA) reacting substances (TBARS) was utilized to measure the quantities of free radicals and lipid peroxidation in placental samples. Under ideal pH and temperature circumstances, this assay quantifies the interaction between TBA and malondialdehyde (MDA), a byproduct of lipid peroxidation. After extracting the complex into an organic solvent (n-butanol), the resultant MDA-TBA adduct was measured spectrophotometrically at 535 nm.

In order to perform the experiment, 2.5 ml of 20% trichloroacetic acid, 1.0 ml of 0.67% TBA, and 0.5 ml of placental homogenate were combined. For thirty (30) minutes, the mixture was incubated at 100°C. Following cooling, 4.0 ml of n-butanol was added, and the mixture was centrifuged for 10 minutes at 5000 rpm after being vortexed for 30 seconds. A spectrophotometer (HUMALYZER JUNIOR) was used to measure the absorbance of the supernatant at 535 nm. Based on an extinction coefficient of 1.56 x 10^5 L mmol^-1 cm^-1, the results were reported in µmol/L (Buege & Aust, 1978).

3.7.3 Placenta Homogenate TAC Test:

The Koracevic approach was used to determine the overall antioxidant status (Koracevic et al., 2001). This method is based on the idea that hydroxyl radicals, or reactive oxygen species, are created when hydrogen peroxide and a standardised solution of Fe-EDTA complex react (Fenton reaction). Benzoate is broken down by these radicals to produce thiobarbiturate-reacting compounds (TBARS). The sample's antioxidants inhibit the synthesis of TBARS. The antioxidant levels in the placenta sample are then determined by spectrophotometrically measuring the decrease in TBARS concentration caused by the presence of antioxidants.

3.7.4 Analytical Procedure;

Following the addition of 20% acetic acid, the Fe–EDTA mixture and H_2O_2 are added to the control sample (A1), (A0, sample blank). With at least three repetitions, a negative control (K1 and K0) was made for each set of studies. It had the same components as A1 or A0, but phosphate buffer was used in place of the placenta homogenate (or other human fluid). UA1 and UA0, a calibration standard containing 1 mmol/litre of uric acid, were used. Pipetting volume (in millilitres) into tubes: After that, the mixture was chilled in an ice bath and incubated for 10 minutes at 100°C (in a boiling water bath). At 532 nm, absorbance was measured in comparison to deionised water.

3.7.5 Calculation:

Antioxidant activity is calculated as follows: POA (mmol/litre) = (CUA) (K — A)/ (K — UA)

Where K = absorbance of control (K1 — K0)

A = absorbance of sample (A1 — A0)

UA = absorbance of uric acid solution (UA1 — UA0)

CUA = concentration of uric acid (in mmol/ litre).

3.7.6 Measurement of Total Peroxide Concentration (TP):

With a few minor adjustments, the FOX2 method (Isong et al., 2022; Miyazawa, 1989) was used to estimate the amounts of total peroxide (TP) (Harma et al., 2005; Yeni et al., 2005). The FOX2 test technique depends on various peroxides found in placenta samples to convert ferrous ions to ferric ions. A coloured ferric-xylenol orange complex is produced by this method, and its absorbance can be measured at 560 nm.

The FOX2 reagent was made by dissolving 9.8 mg of ammonium ferrous sulphate in 10 millilitres of 250 mM H_2SO_4 to get a final concentration of 250 µM ferrous ions in an acidic solution. Then, 90 milliliters of HPLC-grade methanol containing 79.2 mg of butylated hydroxytoluene (BHT) were mixed with this solution. The last working reagent was then prepared as follows: 250 µm ammonium ferrous sulphate, 100 µm xylenol orange, 25 mM H_2SO_4, and 4 mM BHT in 90% vol/vol methanol in a total volume of 100 mL. This was done while stirring. Except for ferrous sulphate, all of the ingredients were included in the blank reagent. A portion of 1800 µl of FOX2 reagent was combined with 200 µl of placenta homogenate. The solution was centrifuged at 12,000 g for 10 minutes following a 30-minute incubation period at room temperature. Using an H_2O_2 solution as a standard, the absorbency of the supernatant was calculated as a function of the absorbency difference between the test and blank tubes. For individual placenta homogenate samples, the coefficient of variance was less than 5%.

3.7.7 Oxidative Stress Index (OSI)

The Oxidative Stress Index (OSI), which indicates the level of oxidative stress, is determined by the percentage ratio of the Total Peroxide (TP) to the Total Antioxidant Capacity (TAC) (Harma et al., 2005; Yanik et al., 2004; Yeni et al., 2005). To calculate the OSI, the unit of TAC, expressed as mmol Trolox equivalent per liter, was converted to μmol equivalent per liter. The OSI value was then calculated using the following formula:

$$OSI = [(TP, \mu mol\ L^{-1})/ (TAC, \mu mol\ Trolox\ equivalent\ L^{-1}) \times 100]$$

3.8.0 BIOCHEMISTRY TESTS AND PRINCIPLES.

Before analysis, the blood samples and frozen placenta homogenates were taken out of the freezer and left to thaw at room temperature. Then, using Envoy® 500 reagents (Vital Diagnostics, USA) by the manufacturer's instructions on the BT 5000® Random Access Chemistry Analyser (Biotecnica, Italy), triglycerides, total cholesterol, and HDL-cholesterol were assessed.

3.8.1 Glucose Test

Hydrogen peroxide (H_2O_2) and gluconic acid are produced when glucose is oxidized enzymatically, a process that is catalysed by glucose oxidase (GOD). The oxidative combination of phenol and 4-aminophenazone (AP), which has maximum absorbance at 505 nm when peroxidase (POD) is present, is initiated by H_2O_2. The process is as follows:

$$Glucose + O_2 + H_2O \xrightarrow{GOD} gluconic\ acid + H_2O_2$$

$$2H_2O_2 + 4AP + phenol \xrightarrow{POD} 4H_2O + 4\text{-}aminophenazone$$

3.8.2 Triglyceride Test

Glycerol is produced by the enzymatic hydrolysis of triglycerides and internal glycerol in the sample. In the presence of ATP and glycerol kinase (GK), glycerol is converted to glycerol phosphate. Phosphate oxidase (GPO) then transforms this resultant glycerol phosphate into hydrogen peroxide (H_2O_2). The 4-amino antipyrine (4-AAP) and p-chlorophenol in the solution react with the H_2O_2 to produce a crimson dye that absorbs light at 510 nm. The presence of potassium ferrocyanide in the solution reduces bilirubin's influence.

Triglycerides + $3H_2O$ $\xrightarrow{\text{Lipase}}$ Glycerol + Fatty Acids

Glycerol + ATP $\xrightarrow{\text{GK}}$ Glycerol phosphate + ADP

Glycerol phosphate + O_2 $\xrightarrow{\text{GPO}}$ Dihydroxyacetone + H_2O_2 + Glycerol

H_2O_2 + p-Chlorophenol + 4-AA $\xrightarrow{\text{POD}}$ $4H_2O$ + 4-p-benzoquinone imine

3.8.3 Total Cholesterol Test:

Cholesterol undergoes enzymatic oxidation through cholesterol esterase (CHOD, EC 1.1.3.6) after the hydrolysis of its esters using a fungal lipase. This process releases hydrogen peroxide, which, in the presence of peroxidase (POD, EC 1.11.1.7), catalyzes the reaction between phenol and 4-aminophenazone (4AP), resulting in the production of quinoneimine, detectable at 500-505nm.

Cholesterol ester $\xrightarrow{\text{lipase}}$ Cholesterol + Fatty acids

Cholesterol+O_2 $\xrightarrow{\text{CHOD}}$ Cholesten-3-+Hydrogen Peroxide

Hydrogen peroxide+4-AP+phenol $\xrightarrow{\text{POD}}$ 4-(p-benzoquinoneimine) +4water

3.8.4 HDL-Cholesterol Test:

By employing phosphotungsten acid for selective precipitation in the presence of magnesium ions, Low-density lipoprotein and very low-density lipoprotein are isolated from high-density

lipoprotein (HDL) cholesterol. Following centrifugation, HDL cholesterol is still present in the supernatant and can be measured with the cholesterol oxidase method.

3.8.5 LDL-Cholesterol Test:

Molecular-weight polymers are used to precipitate LDL specifically, allowing for its isolation from serum. Other lipoproteins (VLDL and HDL) are still present in the supernatant following centrifugation. The enzymatic oxidase/peroxidase method is used to calculate the concentration of the supernatants. By deducting the cholesterol found in the supernatant from the total cholesterol, one can quantify the cholesterol bound to LDL. A 10g/L solution of polyvinyl sulphate dissolved in 25% polyethylene glycol (MW: 600) at a pH of 6.7 serves as the precipitating reagent. As an alternative, Friedewald's equation can be used to determine LDL-cholesterol: Total cholesterol - (triglycerides/5 + HDL) mmol/L equals LDL-cholesterol.

3.8.6. Urea:

The main non-protein nitrogen molecule found in the majority of human bodily fluids is urea. With around 85% of urine nitrogen coming from it, it is the primary byproduct of protein metabolism in humans. As such, it is essential for evaluating renal function as well as the overall control of urea levels in the body. The number of meat sources in the diet, and consequently the metabolism of proteins, as well as the condition of depletion of fluid volume in life (prerenal azotemia) may be strongly associated with urea.

Principle of Urea Test;

Particularly, urea is broken down by urease, releasing ammonia and CO_2. Next, in an alkaline media, the ammonia combines with phenol and hypochlorite to generate indophenol blue,

which is colorimetrically detected at 540 nm. Another name for this procedure is Berthelot's modified reaction.

Urea + H_2O $\xrightarrow{\text{urease}}$ $2NH_3 + CO_2$

3.8.7 Creatinine:

As a consequence of muscle metabolism, creatinine is extremely diffusible and mainly excreted from the body by the kidneys, where the glomerular corpuscle filters it almost completely.

Principle of Creatinine Test:

An alkaline picrate reagent and blood serum combine to generate a yellow-red complex with creatinine. This complex's absorbance is measured at 490 nm. After acidifying the solution, a second reading is obtained to account for non-creatinine chromogens present in the specimen. The Jaffe reaction is the name given to this process.

3.8.8 Total Protein:

Living cells and human life depend on proteins for a variety of functions, including molecular transport, enzyme synthesis, clotting factors, hormone production, and antibody production.

Principle of Total Protein Test

In an alkaline media, peptide bonds in proteins react with Cu^{2+} ions to generate a violet-coloured molecule that absorbs completely at 540 nm. The Biuret reaction, as it is often called, is proportional to the amount of protein present in the blood serum sample.

3.8.9 Albumin:

The most common protein in blood circulation is usually albumin. It is essential for moving both non-food and insoluble food items through the human body's bloodstream's aqueous

medium. Blood osmotic pressure, or oncotic pressure, is strongly correlated with blood serum albumin content, which affects circulatory disorders like oedema.

Principle of Albumin Test

Blood serum Albumin binds with the dye Bromocresol Green (BCG) at a PH of 4.2 to form Serum albumin at a pH of 4.2, interacts with the dye Bromocresol Green (BCG) to produce a complex that absorbs light at a wavelength of 600–630 nm. To prevent non-specific protein binding in the final solution, the resulting solution should be read within 60 seconds.

3.8.10 Bilirubin:

The pigment known as bilirubin is made up of the tetrapyrrole ring. This is created when haemoglobin is broken down into individual haem molecules in the endorecticulocyte systems of the liver, spleen, and marrow. The most common reason for the body's noticeably elevated bilirubin levels is biliary blockage. In haemolytic disorders, the body produces more unconjugated bilirubin than conjugate bilirubin. When biliary blockage occurs, conjugated bilirubin tends to rise.

Principle of Bilirubin Test

In an alkaline environment, bilirubin most precisely combines with diazotised sulphanilic acid to produce azobilirubin, a reddish-violet pigment. Using colorimetry, the colour of this pigment is determined between 530 and 540 nm. Unconjugated bilirubin, also known as free bilirubin, is usually linked to albumin and needs to be dissolved with a solubilizer like caffeine benzoate or 70% ethanol. Conjugated bilirubin reacts readily with the diazo reagent. The Jendrassik (and Grof) method, which measures the total bilirubin resulting from the presence of caffeine, involves the reaction of the drug with diazotised sulphanilic acid.

3.8.11 Aspartate Amino Transferase (AST):

The enzyme aspartate amino transferase (AST) is extensively distributed throughout the tissues of the human body and can be found in the cytoplasm and mitochondria. Patients with liver disorders, especially those with hepatitis in the context of necrosis, have higher levels. Since AST levels indicate the involvement of numerous organ tissues in the body, they cannot be used as a diagnostic test for liver illness.

Principle of Total AST (SGOT) Test

The primary AST-catalysed reaction is shifted in the direction of the production of oxaloacetate (OAA). The rate of NADH oxidation, which is measured between 334 and 366 nm, is related to the activity of AST (SGOT) in the blood serum sample because OAA reacts with malate dehydrogenase (MDH) right away.

L-aspartate +2-oxoglutarate $\xrightarrow{\text{AST}}$ oxaloacetate (OAA) +L-glutamate

OAA + NADH+ H^+ $\xrightarrow{\text{MDH}}$ L-malate + NAD^+

3.8.12 Alanine Aminotransferase (ALT):

Since alanine aminotransferase (ALT) is a cytosolic enzyme, the liver cell's cytoplasm is where it is found.

Principle of ALT (SGPT) Test:

Alanine Aminotransferase (ALT) is the reaction that occurs as follows:

L-Alanine + 2-oxoglutarate $\xrightarrow{\text{ALT}}$ L-glutamate+ pyruvate

3.8.13 Alkaline Phosphatase (ALP):

An enzyme that is extensively present in the human body is called alkaline phosphatase, or ALP. When an enzyme is released from a tissue, its activity can be demonstrated by hydrolysing orthophosphoric acid monoesters in an alkaline media. ALP is produced in

adulthood by the liver, reticuloendothelial system in bone, and the vascular system. These sources produce distinct isoenzymes with elevated serum activities in osteoblasts, which explains why there is a physiologically higher level of ALP at the end of the first trimester of pregnancy. Elevated levels of ALP are seen in pathological diseases such as osteoblastic disease, liver biliary cholestasis, metastatic carcinomas in the bone, and vitamin D malabsorption disorders.

Principle of Alkaline Phosphatase (ALP) Test:

The colourless para nitrophenyl phosphate (pNPP) is hydrolysed by ALP, an orthophosphoric monoester phosphohydrolase, to produce a yellow-coloured p-nitrophenolate and phosphate at pH 9.8, which is detected at 405 nm. In addition to diethanolamine's (DEA) ability to buffer pH, it also plays an active role in the reaction by acting as an acceptor of the phosphate that is released during the following reaction:

P-nitrophenyl phosphate + amino alcohol **ALP** p-nitrophenolate + aminoalkyl phosphate.

3.9 STATISTICAL ANALYSIS.

The statistical software programs MedCalc (v14.8.1.0), GraphPad Prism (v8), and SPSS (v26) were used to analyse the data after they were gathered onto an Excel spreadsheet. Continuous variable normality was assessed using the Kolmogorov-Smirnov test. In SPSS, categorical variables were initially coded before being compiled as frequencies (percent). The standard deviation ± mean was used to express continuous variables. The Chi-Square test or, when appropriate, the Fisher's Exact test were used to evaluate associations between categorical variables. To investigate the correlations between the variables, a Spearman Rank correlation analysis was used. The unpaired t-test (2-tailed) was utilised to ascertain the

variation in the continuous variable distribution across the groups. For parametric variables, Pearson correlation was used to ascertain the link between the maternal factors.

Simple linear regression models were constructed with blood pressure as the independent variable to ascertain the effect of blood pressure on maternal placental characteristics. The Hanley and McNeil technique was used to evaluate the predictive capacities (sensitivity, specificity, etc.) of maternal factors for preeclampsia using the Receiver Operating Characteristic (ROC) curve (Marius & Mbegbu, 2019). All statistical analyses were two-tailed, with a significance level set at $P<0.050$. The significance level for all statistical analyses was set at $P<0.050$, and they were all two-tailed.

3.10 ETHICAL CLEARANCE.

The study complied with the 1964 Declaration of Helsinki or any updated versions of its guidelines for research with human participants. The Navrongo Health Research Centre Institutional Review Board (NHRCIRB378) approved the study. The pregnant women gave written informed permission prior to their involvement in the study. Individuals were free to choose to participate in the study without facing any restrictions because of their political, religious, or cultural identity.

CHAPTER 4

RESULTS

4.1 ASSOCIATION BETWEEN PREECLAMPSIA AND MATERNAL SOCIODEMOGRAPHIC, ANTHROPOMETRIC, OBSTETRIC, AND CLINICAL CHARACTERISTICS.

Table 4.1 revealed that there was no statistically significant difference in gestational age and maternal age between pregnancies complicated by preeclampsia and normotensive pregnancies. On the other hand, BMIs were considerably higher in preeclamptic women than in normotensive women (28.6±6.6 vs. 25.0±4.5; P=0.027).

Table 4. 1: Descriptive statistics of the study population stratified by preeclampsia status

Variable	NP(n=150)	PE(n=100)	*t*	P-value
Maternal age (years)	26.8±6.4	29.4±6.6	-1.389	0.171
Gestational age (weeks)	38.2±1.5	36.4±6.2	1.574	0.122
BMI (Kg/m^2)	25.0±4.5	28.6±6.6	-2.275	0.027
Birth weight (Kg)	3.1±0.6	2.9±0.9	1.081	0.285
Placental length (cm)	20.0±3.4	20.2±5.9	-0.107	0.915
Placental weight (Kg)	0.6±0.2	0.6±0.2	1.032	0.307
BW/PW	5.1±1.2	5.2±1.5	-0.14	0.889
Cord length (cm)	50.1±10.9	52.3±1.0	-0.656	0.515
Cord diameter (cm)	1.2±0.6	1.2±0.5	-0.031	0.975

The results are summarized as mean ± SD. The differences between mean values were determined using an unpaired t-test (2-tailed,), NP; Normotensive Pregnancy, PE; Preeclampsia.

Table 4.2 shows a significant difference in the mode of delivery between women with normotensive pregnancies and those with preeclampsia (χ2=14.275, P<0.001). While the majority of the women with NP had a normal vaginal delivery (86.7%), the majority of those with preeclampsia (PE) had either CS or assisted delivery (65%). In addition, only women diagnosed with PE had preterm birth as compared to those with NP (χ2=12.209, P=0.001). Moreover, PE was associated with abnormal birth outcomes (χ2=12.286,

P<0.001). Lastly, it was discovered that placental malaria was more common in women with PE diagnoses than in those with NP ($\chi 2$=5.335, P=0.032).

Table 4. 2: Sociodemographic, clinical and obstetric categorical variables of the study population

Variable	NP(n=150)	PE(n=100)	$\chi 2$	P-value
Parity			2.824	0.244
Nulliparous	70(46.7)	25(25.0)		
Primiparous	30(20.0)	20(20.0)		
Multiparous	50(33.3)	55(55.0)		
Gravida			1.751	0.237
Primigravida	65(43.3)	25(25.0)		
Multigravida	85(56.7)	75(75.0)		
Anti-malarial prophylaxis			4.787	0.058
No	0(0.0)	15(15.0)		
Yes	150(100)	85(85.0)		
Folic acid			1.531	0.400
No	0(0.0)	5(5.0)		
Yes	150(100)	95(95.0)		
Sickle cell trait			2.219	0.289
No	145(96.7)	85(85.0)		
Yes	5(3.3)	15(15.0)		
Mode of delivery			14.275	<0.001
Normal (vaginal)	130(86.7)	35(35.0)		
CS/Assist	20(13.3)	65(65.0)		
Preterm birth			12.209	0.001
No (≥37)	150(100)	65(65.0)		
Yes (<37)	0(0.0)	35(35.0)		
Birth outcome			14.286	<0.001
Normal	150(100)	60(60.0)		
Abnormal	0(0.0)	40(40.0)		
Cord insertion			4.829	0.090
Central	90(60.0)	85(85.0)		
Paracentral	35(23.3)	15(15.0)		
Others	25(16.7)	0(0.0)		
Peripheral malaria			0.059	0.808
No	140(93.3)	95(95.0)		
Yes	10(6.7)	5(5.0)		
Placental malaria			5.335	0.032
No	145(96.7)	75(75.0)		
Yes	5(3.3)	25(25.0)		

The results are summarized as frequency (per cent). Measures of association were determined using Chi-Square or Fishers exact as appropriate. NP; Normotensive Pregnancy, PE; Preeclampsia.

The complete blood count variables were compared between normotensive pregnancy and preeclampsia as shown in Table 4.3. It was observed that the WBC count was higher in preeclampsia than normotensive pregnancy (14.8±5.1 vs 9.9±01; P<0.001). Similarly, the neutrophil (P=0.005), monocyte (P=0.008), eosinophil (P<0.001) and basophil (P<0.001) counts were higher in preeclampsia than normotensive pregnancy. In addition, preeclampsia was associated with greater neutrophil-to-lymphocyte ratios (NLR) and monocyte-to-lymphocyte ratios (MLR) in comparison to normotensive pregnancies.

Table4. 3: Complete blood count variables in preeclampsia and normotensive pregnancy

Variable	**NP(n=150)**	**PE(n=100)**	***t***	**P-value**
WBC x 10^3/µL	9.9±01	14.8±5.1	-5.267	<0.001
RBC x 10^6/µL	3.9±0.1	3.8±0.4	1.035	0.306
HGB (g/dL)	10.7±0.9	10.1±1.6	1.619	0.112
HCT (%)	31.8±2.9	30.9±4.6	0.832	0.410
MCV (fL)	82.5±7.6	82.3±7.0	0.083	0.934
MCH (pg/L)	28.2±2.6	26.9±2.6	1.604	0.115
MCHC (g/dL)	33.7±1.4	32.7±2.4	1.800	0.078
PLT x 10^3/µL	205±45	204±83	0.026	0.979
NEUT (%)	76.1±5.8	81.8±6.6	-3.200	0.002
LYMP (%)	15.4±4.6	8.7±4.3	5.199	<0.001
MONO (%)	6.5±2.8	8.3±1.2	-2.776	0.008
EOSIN (%)	0.1±0.06	0.6±0.48	-5.211	<0.001
BASO (%)	0.3±0.15	0.6±0.17	-5.774	<0.001
NLR	5.5±2.3	12.3±7.0	-4.883	<0.001
MLR	0.4±0.19	1.3±0.81	-5.457	<0.001

The results are presented in mean ± SD and were compared for differences using an unpaired t-test (2-tailed). NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte--to-lymphocyte ratio., NP; Normotensive Pregnancy, PE; Preeclampsia.

4.2 THE PREDICTIVE ACCURACIES OF BLOOD CELL INDICES FOR PREECLAMPSIA

The diagnostic ability of white blood cell indices for preeclampsia was determined (Figure 3 and 4) and also compared (Figure 5). Both NLR and MLR were potential predictors of preeclampsia ($P<0.001$). But MLR's area under the curve (AUC) was higher than NLR's (0.89 versus 0.85). At 85.0% and 83.3%, respectively, the sensitivity and specificity of NLR were attained at an associated criterion of >7.42 while MLR had a sensitivity of 85.0% and a specificity of 83.3% at an associated criterion of ≤0.61. It was observed that MLR was more sensitive than NLR; however, their specificities were comparable.

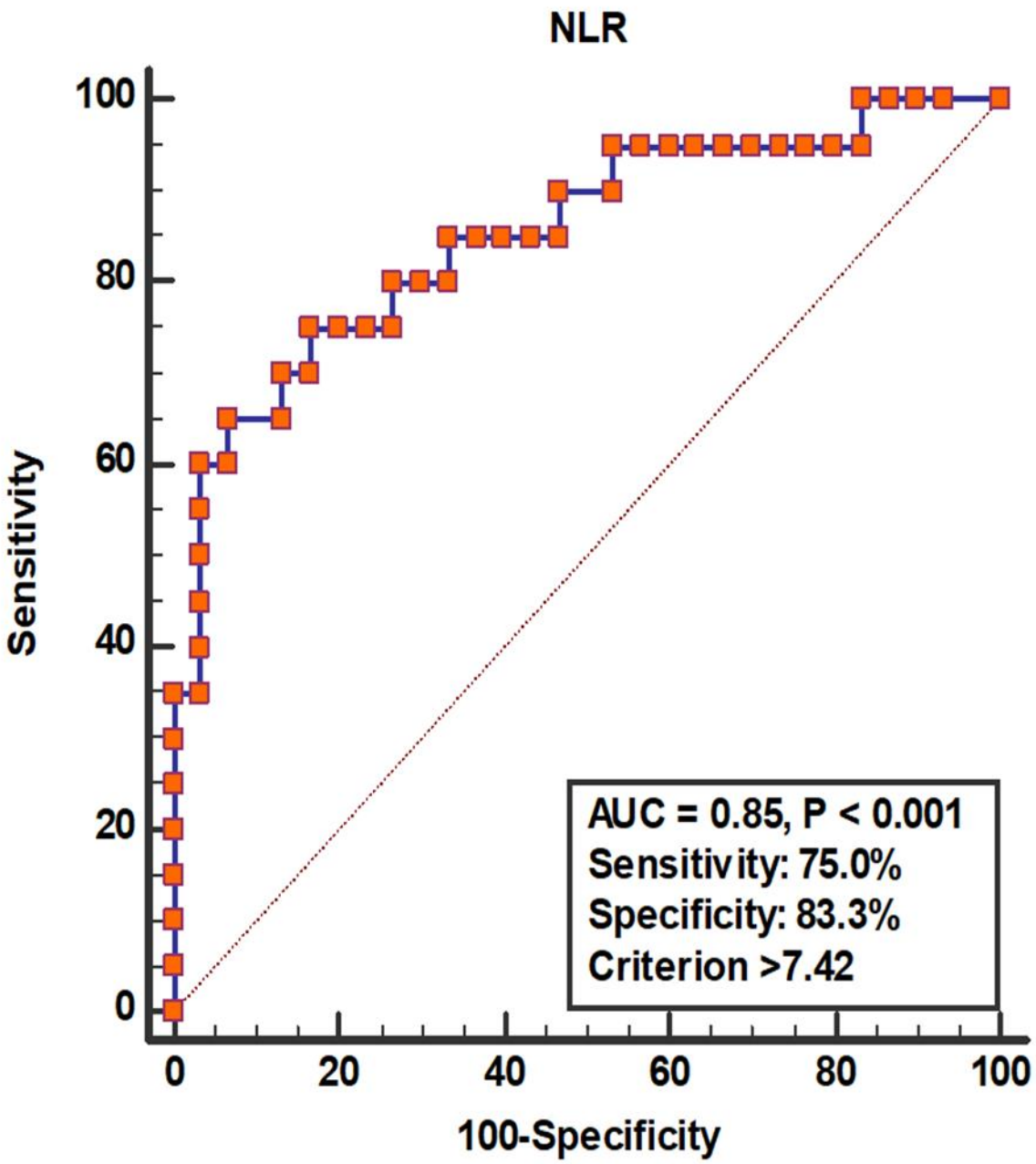

Figure 3: Shows the diagnostic ability of neutrophil-to-lymphocyte ratio *(NLR) for preeclampsia. AUC: area under the curve.*

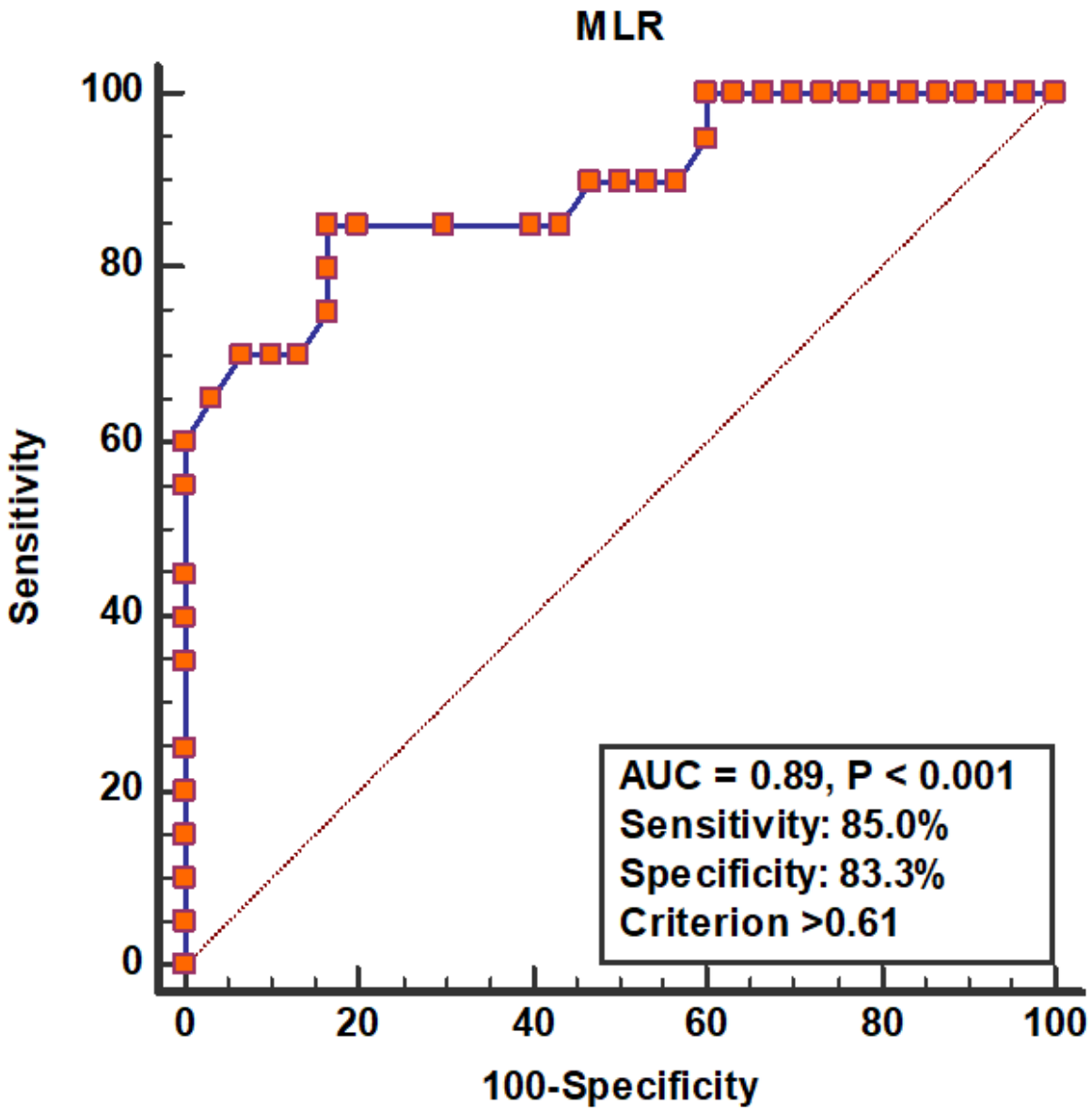

Figure 4: ***Shows the diagnostic ability of monocyte-to-lymphocyte ratio (MLR) for preeclampsia. AUC: area under the curve***

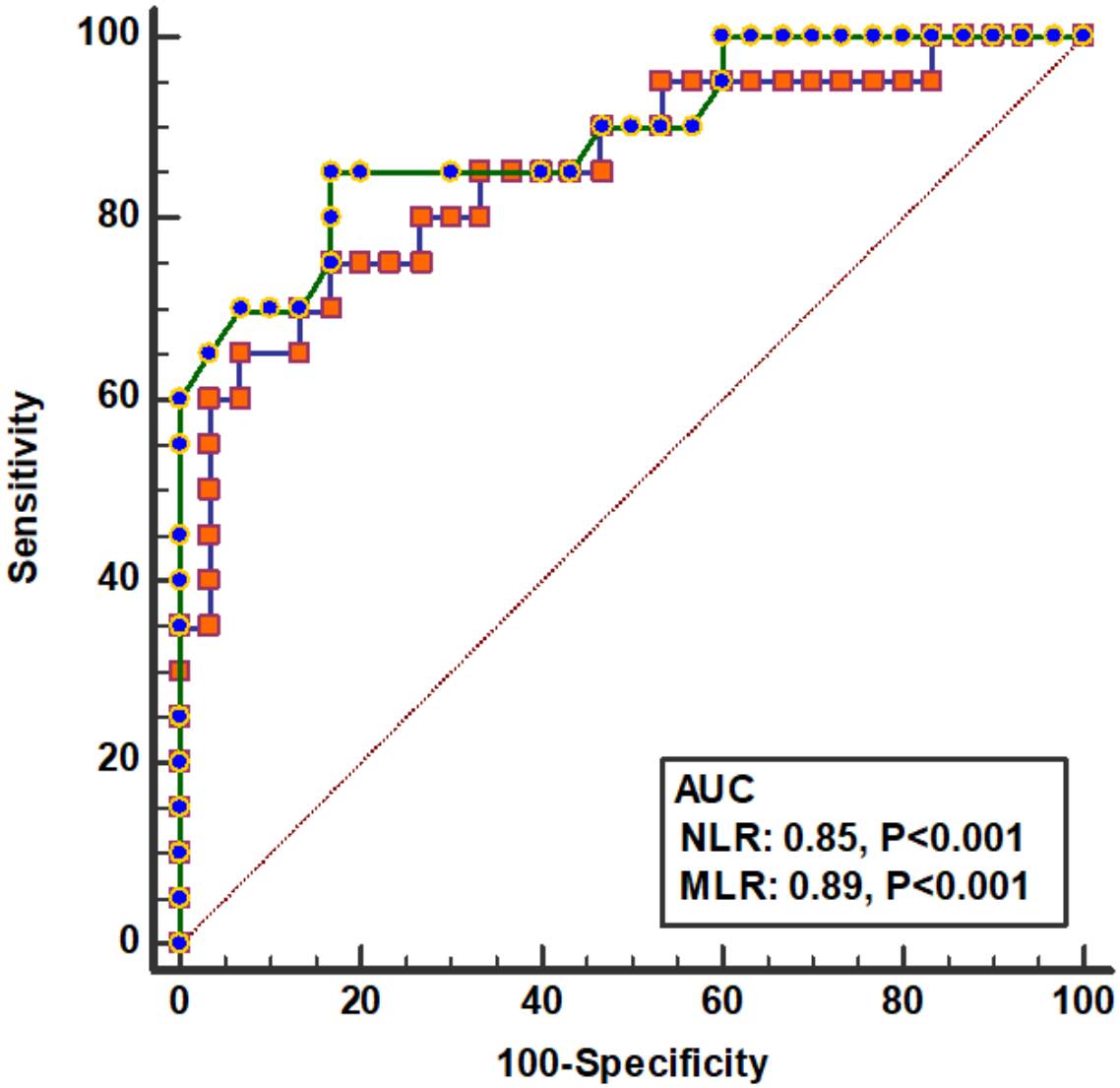

Figure 5: ***The comparison of Receiver Operator Characteristic (ROC) curves of blood cell indices in predicting preeclampsia. NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio***

4.3 THE IMPACT OF BLOOD PRESSURE ON THE LEVELS OF PLACENTAL OXIDATIVE STRESS MARKERS.

The effect of blood pressure on the placenta's levels of oxidative stress markers was assessed. (Table 4.4). All oxidative stress markers were found to be impacted by blood pressure, except placental total peroxide levels. Varying between 8.3% and 65.3% (adjR2 =0.083-0.653) in the levels of placental oxidative stress indicators was explained by the combined influence of systolic and diastolic blood pressure.

The total antioxidant capacity was the most impacted by blood pressure while MDA was the least impacted (adjR^2:0.653 vs 0.083). It was also observed that the addition of diastolic to systolic blood pressure in a multivariable analysis did not markedly have an influence on the concentrations of indicators of placental oxidative stress. The majority of the variation in the levels of placental oxidative stress indicators may be explained by systolic blood pressure

Table 4. 4: Impact of blood pressure on placental oxidative stress markers in the total sample

Variable	Equation (x_1=SBP; x_2=DBP)	R	R^2	adjR^2	SEE	P-value
pMDA	y=4.134+0.062 x_1	0.319	0.102	0.083	5.132	0.024
	y=4.464-0.028 x_1+0.141 x_2	0.381	0.145	0.109	5.060	0.025
pTAC	y=27.034-0.123 x_1	0.812	0.659	0.652	2.457	<0.001
	y=26.922-0.092 x_1-0.048 x_2	0.817	0.667	0.653	2.453	<0.001
pCAT	y=12.948-0.053 x_1	0.457	0.209	0.192	2.876	<0.001
	y=12.859-0.029 x_1-0.038 x_2	0.467	0.218	0.184	2.890	0.003
pTP	y=21.402+0.008 x_1	0.025	0.001	-0.020	8.738	0.886
	y=20.913+0.141 x_1-0.208 x_2	0.193	0.037	-0.004	8.667	0.411
pOSI	y=-1.653+0.031 x_1	0.573	0.328	0.314	1.237	<0.001
	y=-1.666+0.035 x_1-0.006 x_2	0.573	0.329	0.300	1.249	<0.001

Linear regression (LR) models with markers of oxidative stress (y) as the dependent and diastolic blood pressure (DBP) as the independent variable. NP: normotensive pregnancy preeclampsia, PE: preeclampsia, p: placenta, UA: uric acid, MDA: malondialdehyde, TAC: total antioxidant capacity, CAT: catalase, TP: total peroxide, OSI: oxidative stress index.

Preeclampsia was substantially less likely to have placental levels of AST, CRT, uric acid, TAC, and CAT than normotensive pregnancy (P<0.050). On the other hand, preeclampsia was associated with higher placental MDA (P=0.001) and OSI (P<0.001) than normotensive pregnancy (Table 4.5).

Table 4. 5 : Comparison of placental biochemistry variables between normotensive pregnancy and preeclampsia.

Variable	NP(n=150)	PE(n=100)	*t*	P-value
pTCHOL (mmol/L)	0.93±0.22	0.9±0.26	0.435	0.666
pHDL(mmol/L)	0.05±0.02	0.05±0.02	0.000	1.000
pLDL (mmol/L)	0.17±0.13	0.16±0.10	0.424	0.674
pVLDL (mmol/L)	0.66±0.16	0.63±0.21	0.500	0.619
pTRIG (mmol/L)	1.86±0.45	1.80±0.59	0.412	0.682
pAST (IU/L)	19.9±14.9	11.0±7.5	2.459	0.018
pALT (IU/L)	12.5±3.6	13.1±5.4	-0.499	0.620
pUREA (mmol/L)	11.9±2.4	12.9±4.7	-0.992	0.326
pCRT (µmol/L)	36.6±15.3	24.9±6.1	3.232	0.002
pBUN (mmol/L)	2.0±0.4	2.2±0.8	-1.001	0.322
pUric acid (mgdL)	17.8±6.4	14.2±5.1	2.126	0.039
pMDA (nmol/L)	10.4±4.5	15.2±5.4	-3.414	0.001
pTAC (mmol/L)	14.1±1.8	6.5±2.3	13.157	<0.001
pCAT (IU/L)	6.9±2.9	4.7±3.3	2.480	0.017
pTP (mmol/L)	22.0±9.6	23.0±7.1	-0.374	0.710
pOSI	1.6±0.7	4.3±2.5	-5.712	<0.001

The results are presented as mean ± SD. Mean values were compared using an unpaired t-test (2-tailed) p: placental.

4.4 THE PREDICTIVE ACCURACIES OF PLACENTAL OXIDATIVE STRESS MARKERS FOR PREECLAMPSIA

As shown in Table 4.6, the placental levels of MDA and OSI were significantly higher in preeclampsia (P < 0.001, P = 0.048, P = 0.001, and P < 0.001, respectively). In contrast, the placental levels of TAC and CAT were found to be lower in preeclampsia compared to normotensive pregnancies (P < 0.001 and P = 0.017, respectively).

Table 4. 6: Comparison of placental biochemistry variables between normotensive pregnancy and preeclampsia

Variable	NP(n=150)	PE(n=100)	*t*	P-value
pMDA (nmol/L)	10.4±4.5	15.1±5.4	-3.414	0.001
pTAC (mmol/L)	14.0±1.6	6.5±2.3	13.757	<0.001
pCAT (IU/L)	6.9±2.9	4.7±3.3	2.480	0.017
pTP (mmol/L)	22.0±9.6	23.0±7.1	-0.374	0.710
pOSI	1.6±0.7	3.7±1.5	-6.577	<0.001

The results are presented as mean ± SD. The differences between groups were compared using an unpaired t-test (2-tailed) p: placental

Results from Figures 6 to 10 show that only the placental levels of MDA, TAC, CAT, and TP demonstrated significant predictive potential in the diagnosis of preeclampsia (P<0.001, 0.019, <0.001, <0.001 and 0.010 respectively). However, placental catalase activity was most predictive variable with a perfect area under the curve at 1.0 with both sensitivity and specificity at 100%.

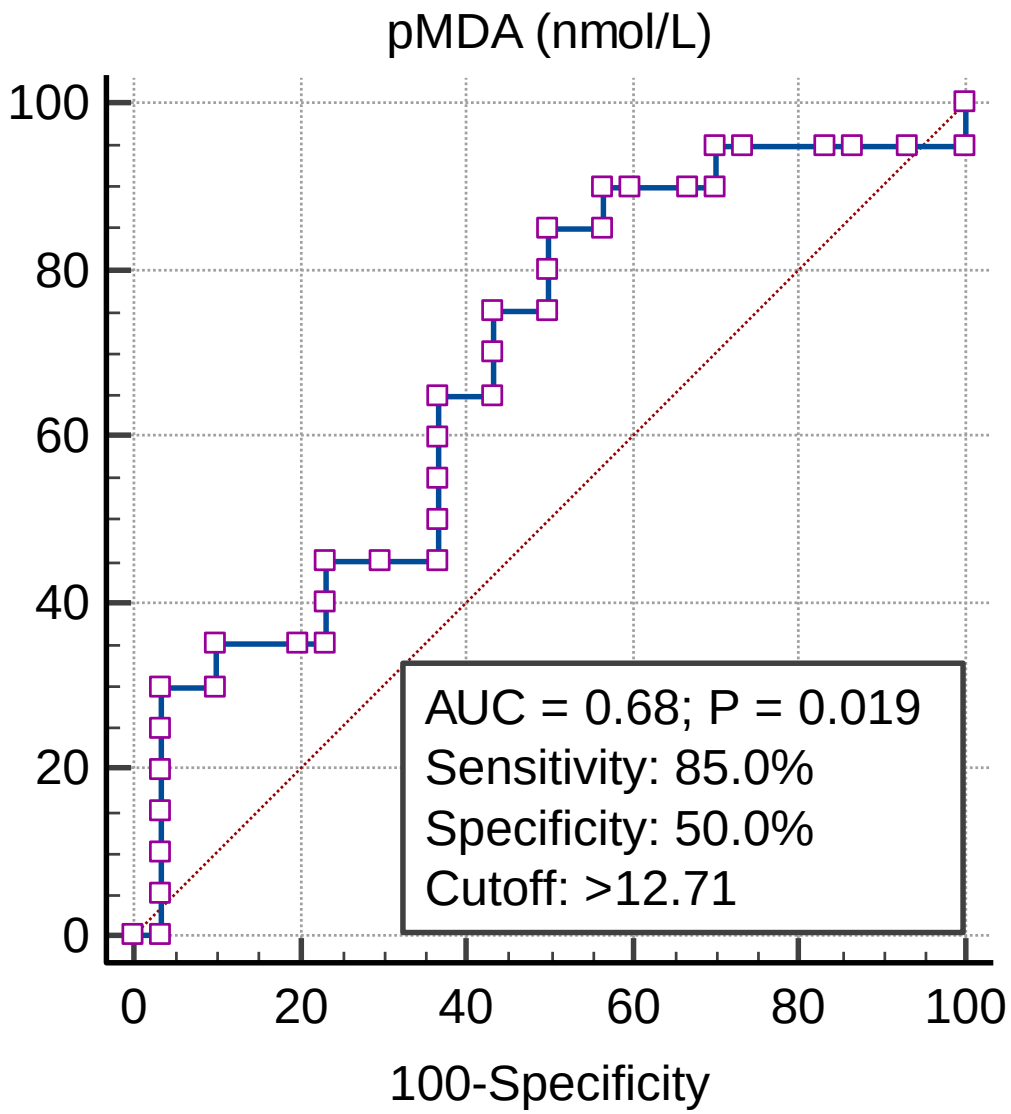

Figure 6: ***The receiver operator characteristic curve showing the predictive ability of placental malondialdehyde (pMDA) in the diagnosis of preeclampsia***

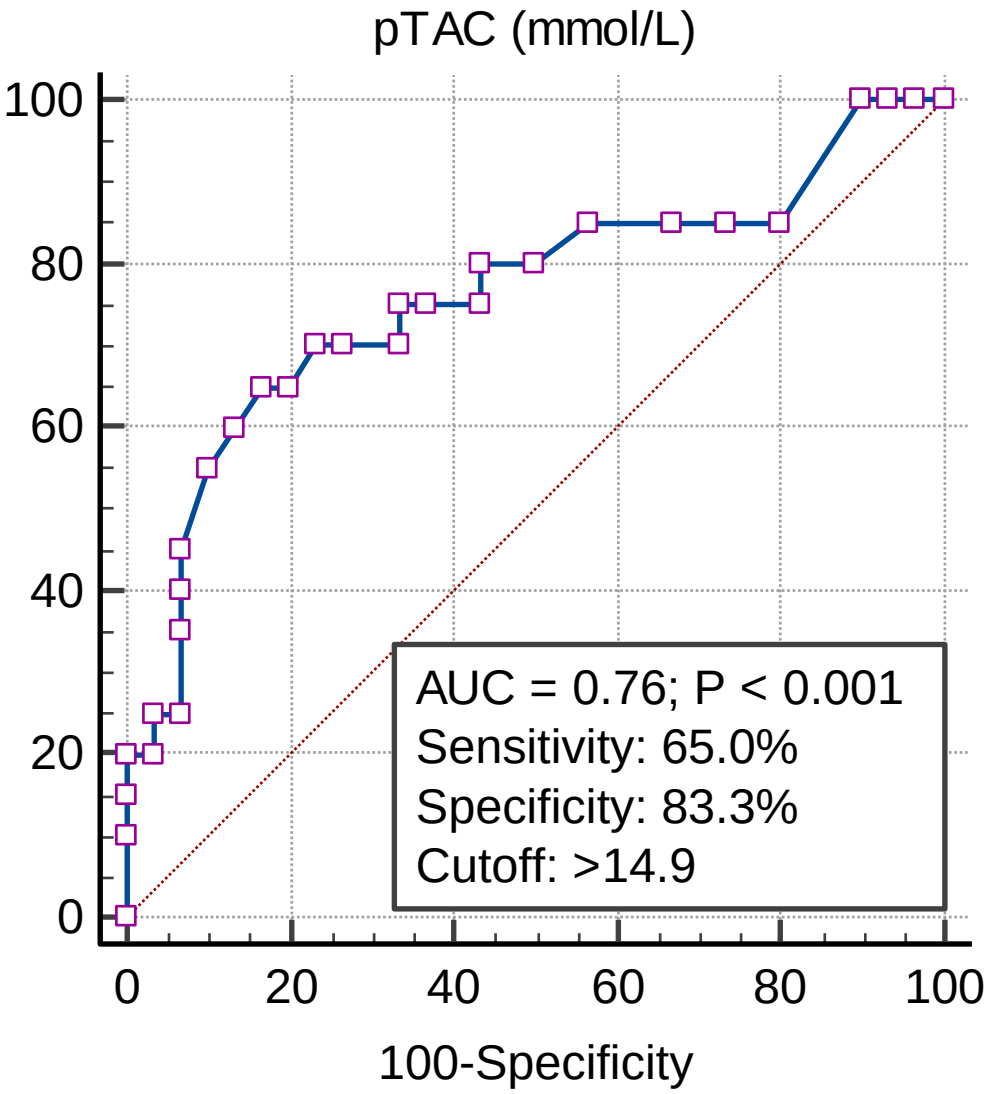

Figure 7: ***The receiver operator characteristic curve showing the predictive ability of placental total antioxidant capacity (pTA)C in the diagnosis of preeclampsia***

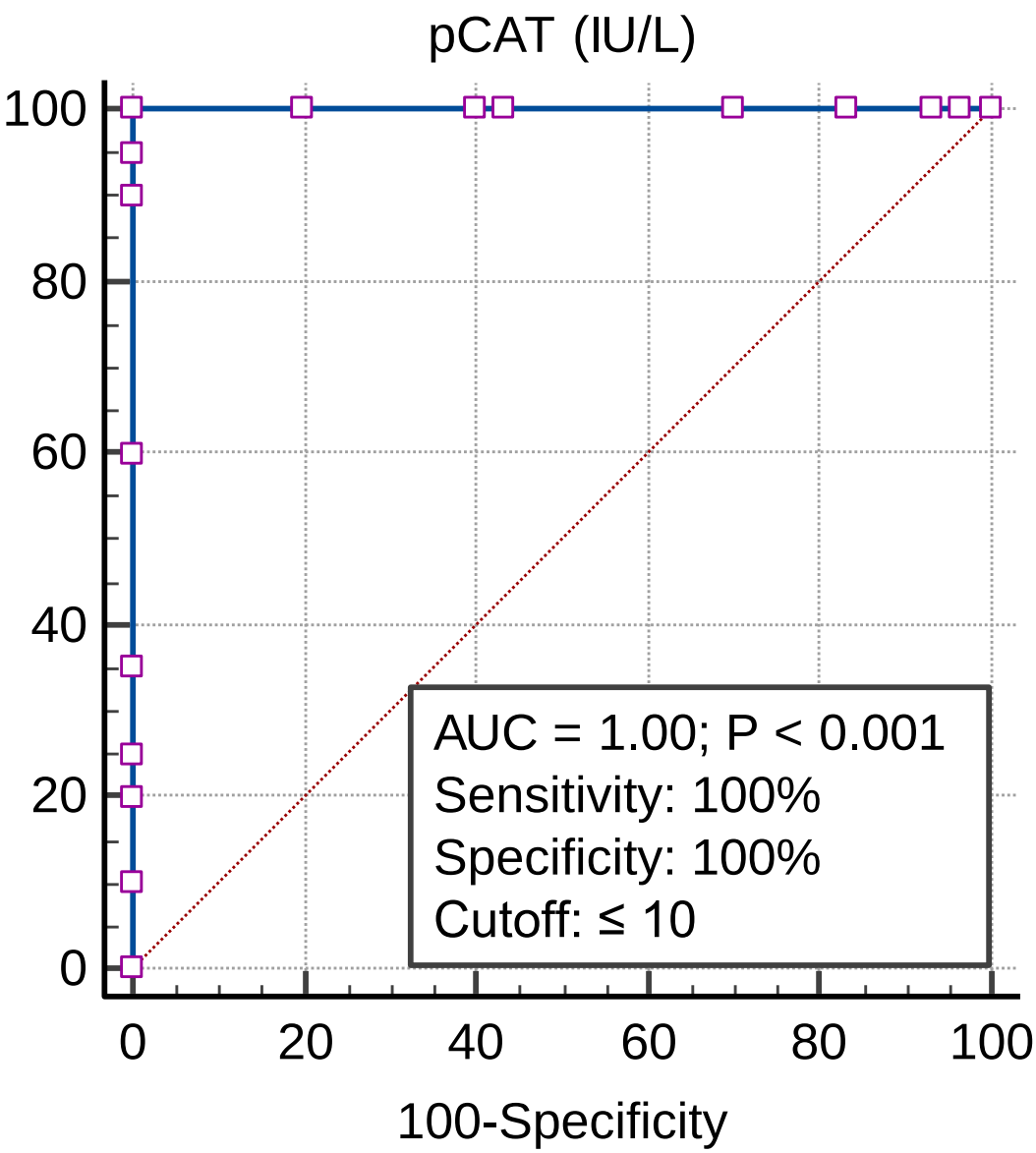

Figure 8: *The receiver operator characteristic curve showing the predictive ability of placental catalase activity (pCAT) in the diagnosis of preeclampsia*

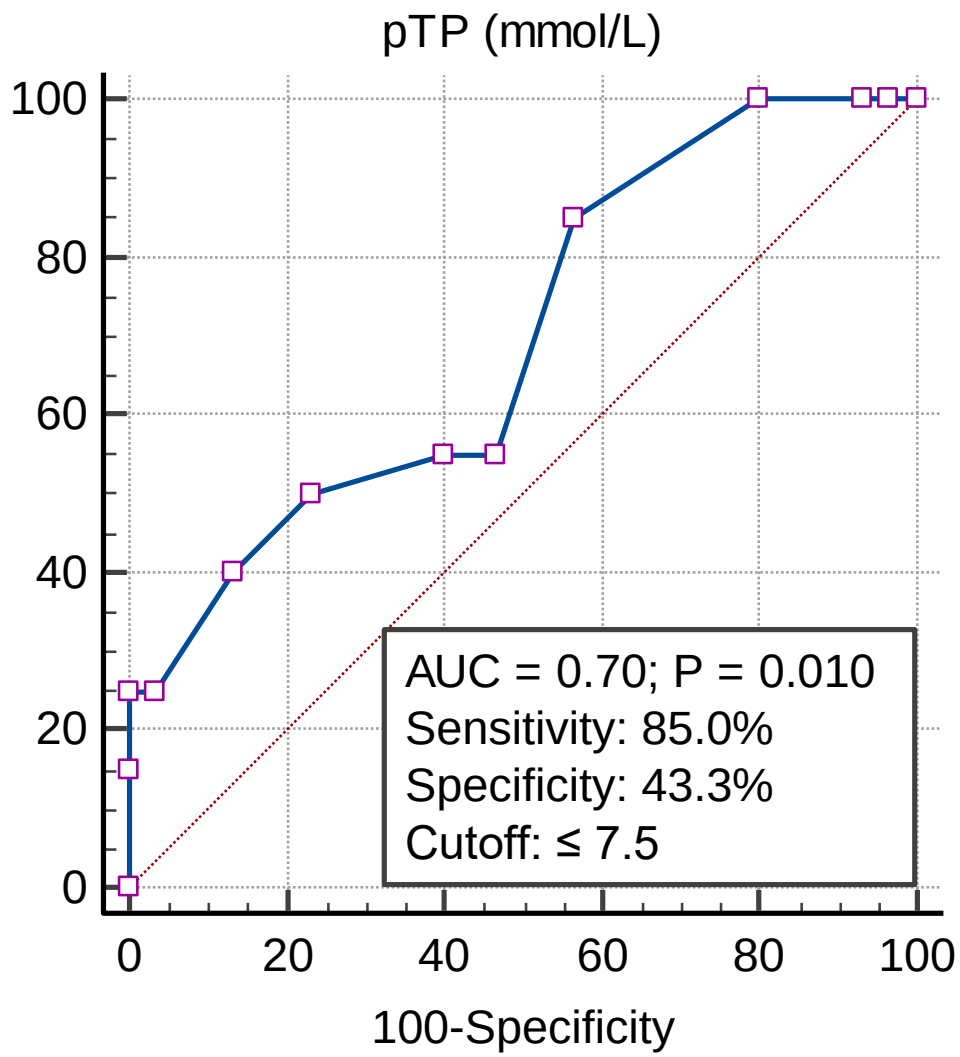

Figure 9: ***The receiver operating characteristic (ROC) curve illustrates the predictive ability of placental total peroxide (pTP) in diagnosing preeclampsia.***

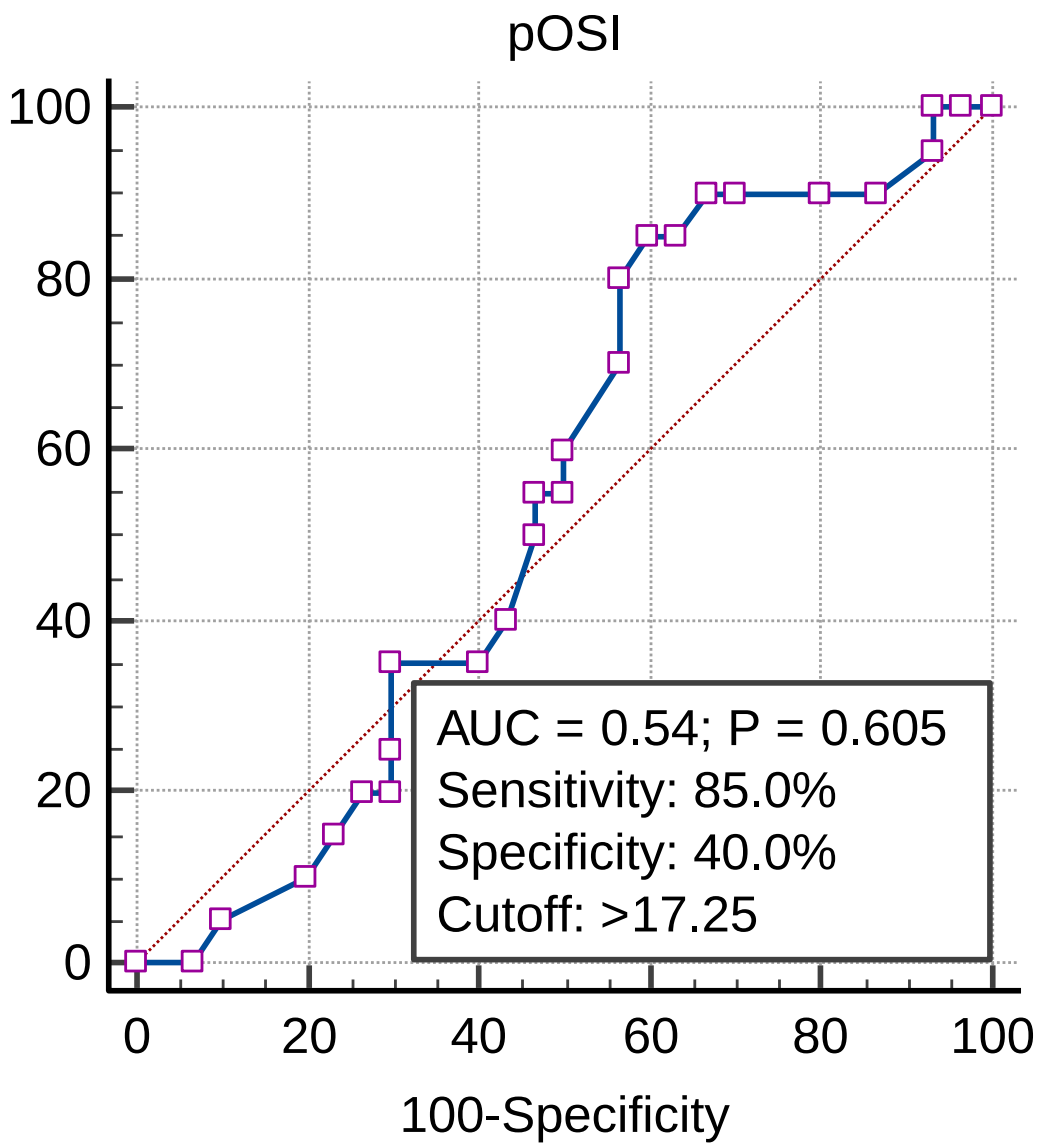

Figure 10: ***The receiver operator characteristic curve showing the predictive ability of placental oxidative stress index (pOSI) in the diagnosis of preeclampsia***

4.5 THE PREDICTIVE ACCURACIES OF PLACENTAL AND SERUM BIOCHEMISTRY VARIABLES FOR PREECLAMPSIA

The placental levels of lipids, liver enzymes and renal function variables were compared (Table 4.7). The placental level of creatinine was higher in preeclampsia than normotensive pregnancy (41.9±10.5 vs 24.6±0.3; P<0.001). Similarly, the placental uric acid level was higher in preeclampsia than in normotensive pregnancy (16.6±4.4 vs 13.9±4.8; P=0.048).

Table 4. 7: Predictive accuracies of placental biochemistry variables for diagnosis of preeclampsia

Variable	NP(n=150)	PE(n=100)	*t*	P-value
pTCHOL (mmol/L)	1.0±0.1	0.9±0.3	1.020	0.313
pHDL(mmol/L)	0.1±0.0	0.1±0.0	0.036	0.972
pLDL (mmol/L)	0.2±0.1	0.2±0.1	0.424	0.674
pVLDL (mmol/L)	0.7±0.2	0.6±0.2	0.500	0.619
pTRIG (mmol/L)	1.9±0.4	1.8±0.6	0.412	0.682
pAST (IU/L)	10.2±5.8	8.1±2.8	1.540	0.130
pALT(IU/L)	12.2±2.4	13.1±5.4	-0.749	0.457
pUREA (mmol/L)	11.9±2.4	11.9±2.4	-0.992	0.326
pCRT (µmol/L)	24.6±0.3	41.9±10.5	-9.072	<0.001
pBUN (mmol/L)	2.0±0.4	2.2±0.8	-1.001	0.322
pUric acid (mgdL)	13.9±4.8	16.6±4.4	-2.028	0.048

The results are presented as mean ± SD. The differences between groups were compared using an unpaired t-test (2-tailed) p: placental

A comparison was made between the serum levels of lipids, liver enzymes, and renal function factors (Table 4.8). According to the findings, preeclampsia is linked to increased levels of uric acid (P<0.001), aspartate aminotransferase (P<0.001), alanine aminotransferase (P<0.001), urea (P=0.016), creatinine (P=0.049), blood urea nitrogen (P=0.014), and serum total cholesterol (P=0.040). Preeclampsia was associated with reduced serum levels of high-density lipoprotein cholesterol and an estimated glomerular filtration rate.

Table 4. 8: Predictive accuracies of placental biochemistry variables for diagnosis of preeclampsia

Variable	NP(n=150)	PE(n=100)	*t*	P-value
TCHOL (mmol/L)	4.3±0.4	4.7±1.0	-2.115	0.040
HDL (mmol/L)	1.0±0.1	0.8±0.2	2.363	0.022
LDL (mmol/L)	2.5±0.4	3.3±0.7	-6.013	<0.001
VLDL (mmol/L)	0.7±0.2	0.6±0.2	1.333	0.189
TRIG (mmol/L)	1.9±0.4	1.8±0.6	1.241	0.221
AST (IU/L)	56.3±29.6	126.2±38.6	-7.234	<0.001
ALT (IU/L)	45.8±8.5	81.7±19.5	-8.927	<0.001
UREA (mmol/L)	30.3±8.4	35.6±9.1	-2.485	0.016
CRT (µmmol/L)	63.3±16.1	71.0±6.0	-2.023	0.049
BUN (mmol/L)	5.0±1.4	6.1±1.6	-2.548	0.014
Uric acid (mg/dL)	5.1±2.0	10.7±6.5	-4.45	<0.001
eGFR (min/mL/1.73m^2	103±20	102±11	2.173	0.035

The results are presented as mean ± SD. The differences between groups were compared using an unpaired t-test (2-tailed).

The relationship between biochemistry variables obtained from the placenta and serum were determined in normotensive pregnancy (Table 4.9) and also in preeclampsia (Table 4.10). It was observed that biochemistry variables from the placenta did not significantly correlate with same variable from the serum in both normotensive pregnancy and preeclampsia.

Table 4. 9: Correlation between blood and placental biochemistry variables in normotensive pregnancy

Variable	pTCOL	pHDL	pLDL	pVLDL	pTRIG	pAST	pALT	pUREA	pCRT	pBUN	pUA
TCOL (mmol/L)	-0.284	0.088	0.258	-0.130	-0.128	0.405*	-0.046	-0.141	0.17	-0.138	0.011
HDL (mmol/L)	0.063	-0.066	0.144	0.331	0.332	-0.023	-0.154	0.141	-0.073	0.143	-0.103
LDL (mmol/L)	0.108	0.021	0.26	0.062	0.066	0.097	-0.056	-0.24	0.231	-0.238	-0.095
VLDL (mmol/L)	-0.213	0.143	0.253	-0.264	-0.262	0.321	-0.016	-0.299	0.197	-0.294	0.086
TRIG (mmol/L)	-0.231	0.104	0.216	-0.296	-0.294	0.312	-0.015	-0.336	0.173	-0.331	0.054
AST (IU/L)	-0.269	-0.157	-0.015	-0.043	-0.048	0.285	-0.189	-0.118	0.208	-0.123	-0.056
ALT (IU/L)	-0.034	-0.063	-0.444*	-0.36	-0.362*	-0.114	-0.254	-0.134	0.060	-0.134	-0.181
UREA (mmol/L)	0.112	0.279	-0.072	-0.056	-0.06	-0.237	-0.159	0.312	-0.180	0.317	0.061
CRT (µmol/L)	0.355	-0.085	-0.001	0.299	0.302	0.136	0.236	0.361*	-0.026	0.366*	0.064
BUN (mmol/L)	0.110	0.305	-0.093	-0.088	-0.091	-0.243	-0.186	0.299	-0.209	0.304	0.043
UA (mg/dL)	0.066	0.056	0.110	0.066	0.063	0.283	-0.147	0.042	0.189	0.045	0.021

The results are presented as partial correlation coefficients that were adjusted for BMI and gestational age. *P<0.050

Table 4. 10: Correlation between blood and placental biochemistry variables in preeclampsia

	Ptcol	pHDL	pLDL	pVLDL	pTRIG	Past	pALT	pUREA	pCRT	pBUN	pUA
TCOL (mmol/L)	-0.142	0.006	-0.101	-0.218	-0.209	0.099	-0.115	-0.028	0.045	-0.028	0.313
HDL (mmol/L)	-0.385	-0.175	-0.186	-0.470*	-0.452*	0.473*	-0.384	-0.221	0.472*	-0.221	0.645**
LDL (mmol/L)	0.383	0.275	-0.161	0.262	0.273	0.090	0.283	0.476*	-0.214	0.476*	0.114
VLDL (mmol/L)	0.148	0.239	0.054	0.035	0.034	-0.254	0.000	0.167	-0.197	0.166	0.049
TRIG (mmol/L)	0.141	0.234	0.057	0.030	0.029	-0.252	-0.009	0.159	-0.192	0.158	0.050
AST (IU/L)	0.137	0.016	0.278	0.091	0.091	-0.392	0.231	0.322	-0.576**	0.322	-0.199
ALT (IU/L)	0.259	-0.183	0.222	0.003	0.027	0.291	0.139	0.361	0.187	0.361	0.313
UREA (mmol/L)	0.340	-0.164	0.185	0.159	0.168	-0.101	0.329	0.378	-0.213	0.378	0.148
CRT (µmol/L)	-0.171	-0.061	-0.130	-0.127	-0.128	-0.193	-0.136	-0.087	-0.011	-0.086	0.341
BUN (mmol/L)	0.324	-0.164	0.192	0.148	0.157	-0.102	0.315	0.352	-0.208	0.352	0.149
UA (mg/dL)	-0.083	-0.127	0.376	0.047	0.032	-0.083	0.112	0.164	-0.413	0.164	-0.123

The results are presented as partial correlation coefficients that were adjusted for BMI and gestational age. *P<0.050, **P<0.010

Results from Figures 11 to 20 show that only the placental levels of creatinine, MDA, TAC, CAT and TP demonstrated significant predictive potential in the diagnosis of preeclampsia (P<0.001, 0.019, <0.001, <0.001 and 0.010 respectively). However, placental catalase activity was most predictive variable with a perfect area under the curve at 1.0 with both sensitivity and specificity at 100%.

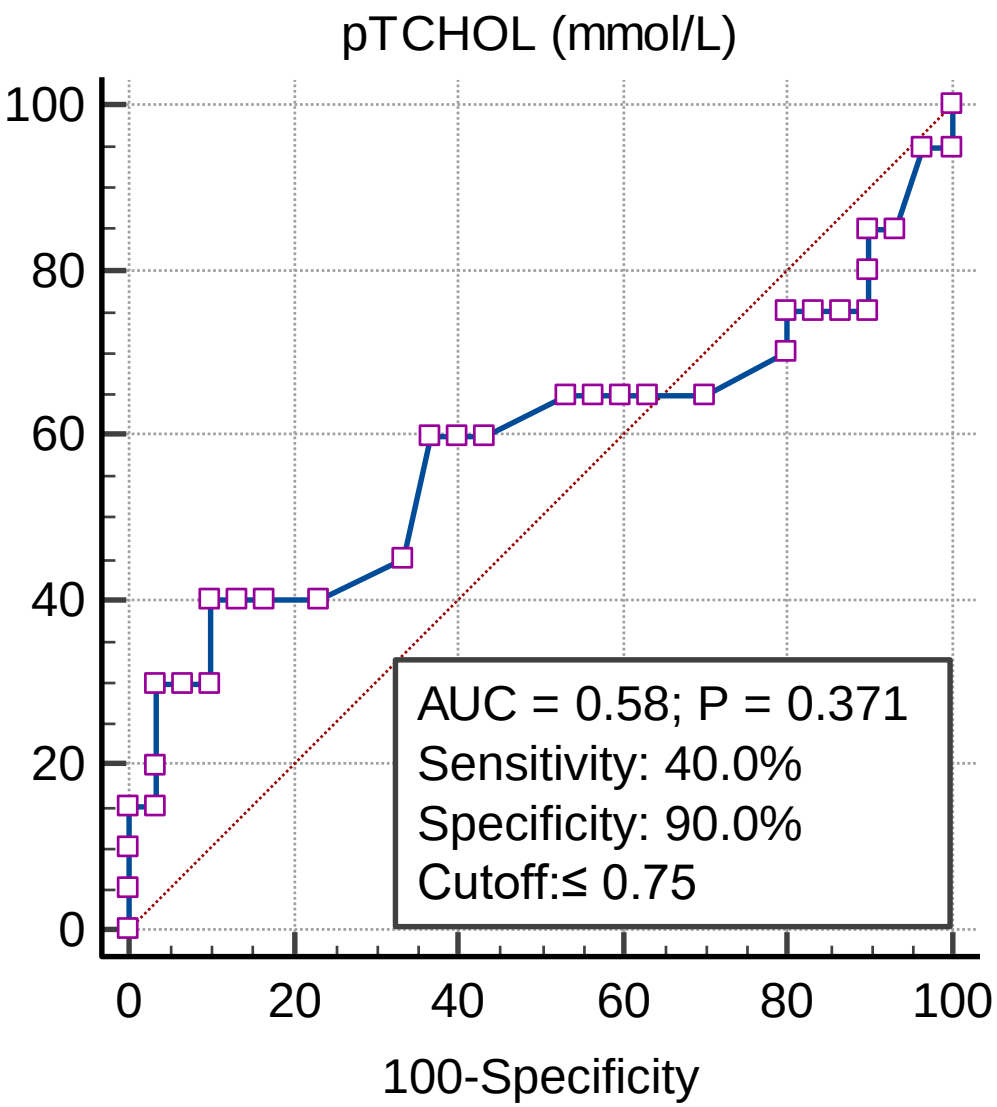

Figure 11: ***The receiver operator characteristic curve shows the predictive ability of placental total cholesterol (pTCHOL) in the diagnosis of preeclampsia.***

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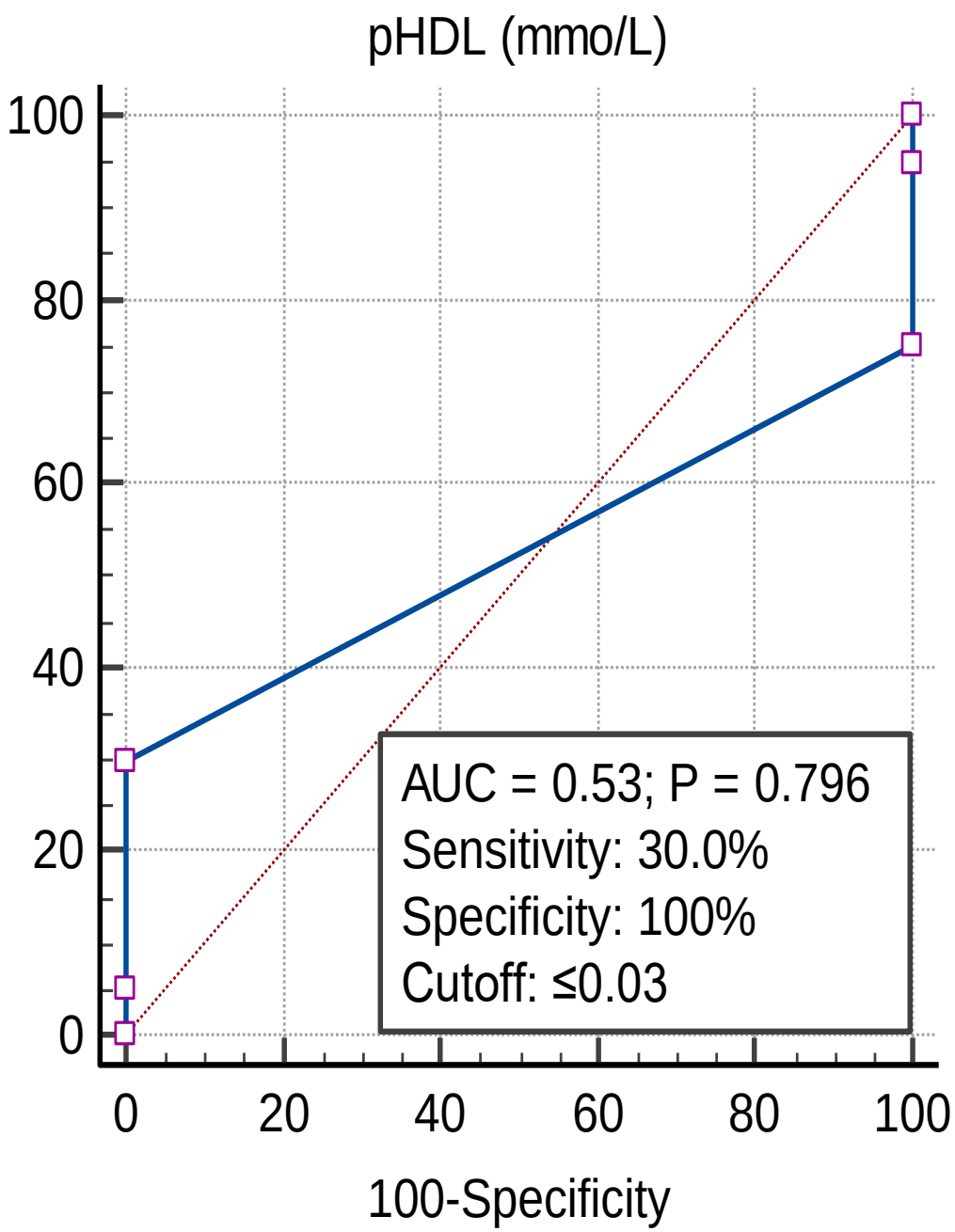

Figure 12: ***The receiver operator characteristic curve shows the predictive ability of placental high-density lipoprotein (pHDL) cholesterol in the diagnosis of preeclampsia***

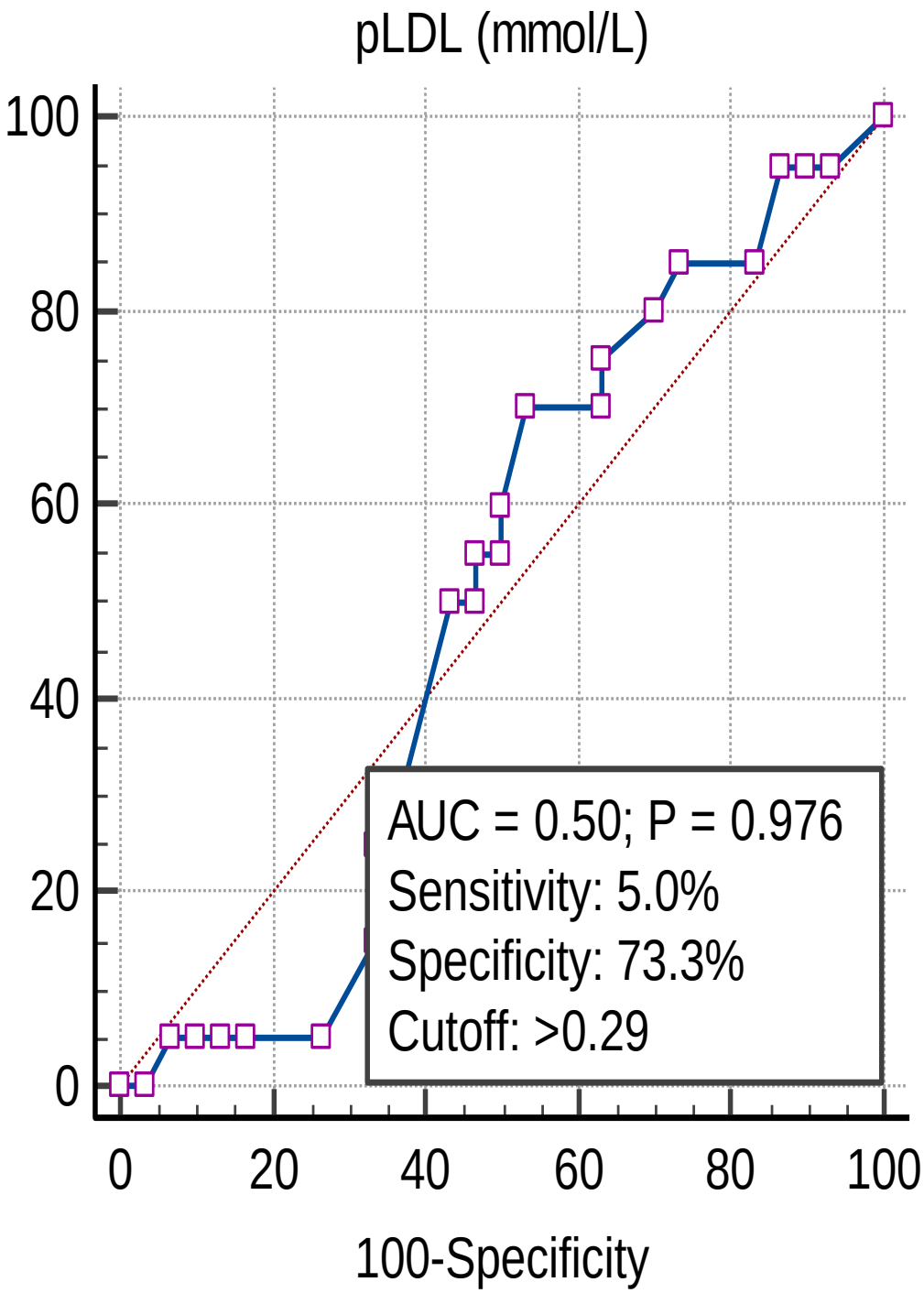

Figure 13: ***The receiver operator characteristic curve shows the predictive ability of placental low-density lipoprotein (pLDL) cholesterol in the diagnosis of preeclampsia***

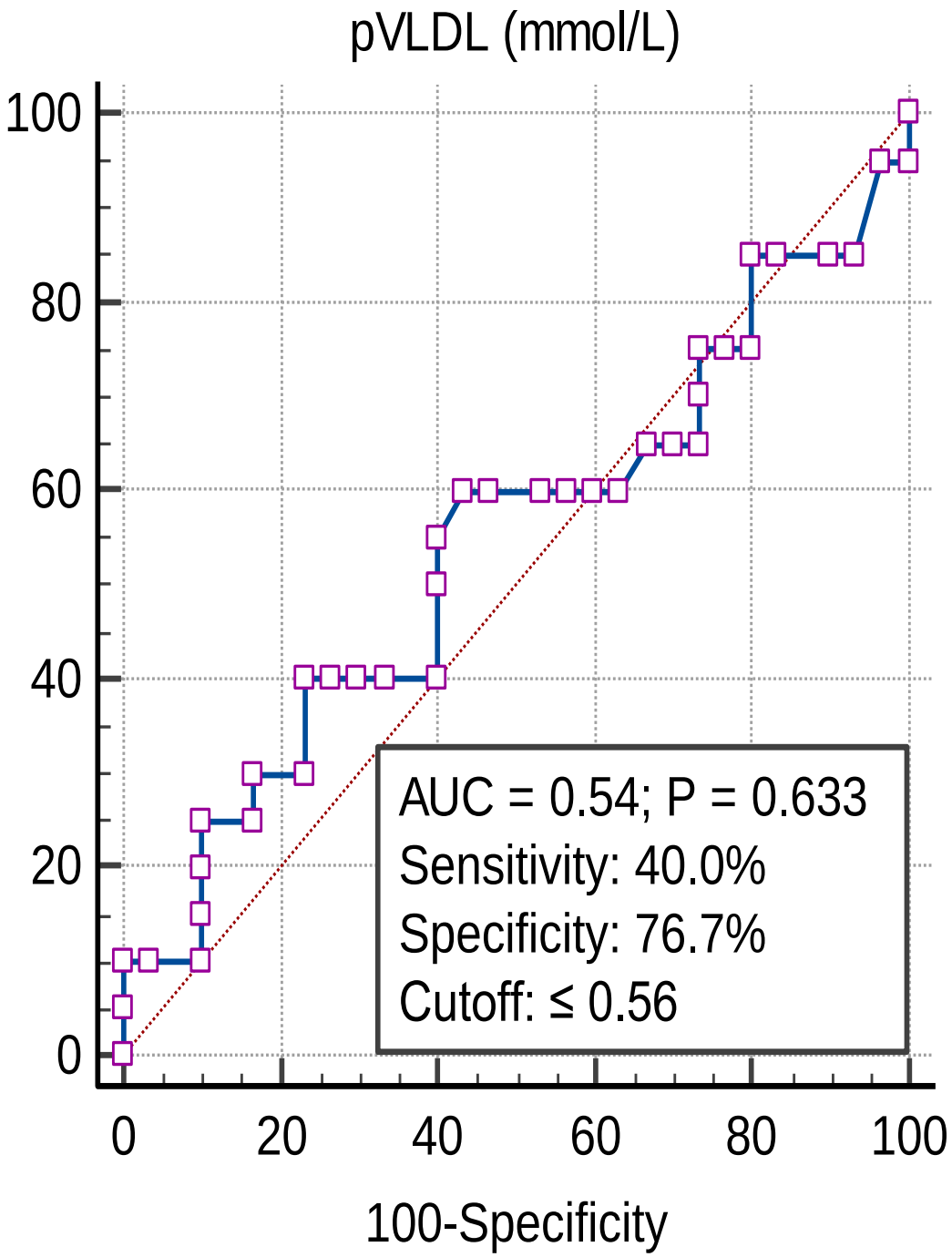

Figure 14: ***The receiver operator characteristic curve shows the predictive ability of placental very low-density lipoprotein (pVLDL) cholesterol in the diagnosis of preeclampsia.***

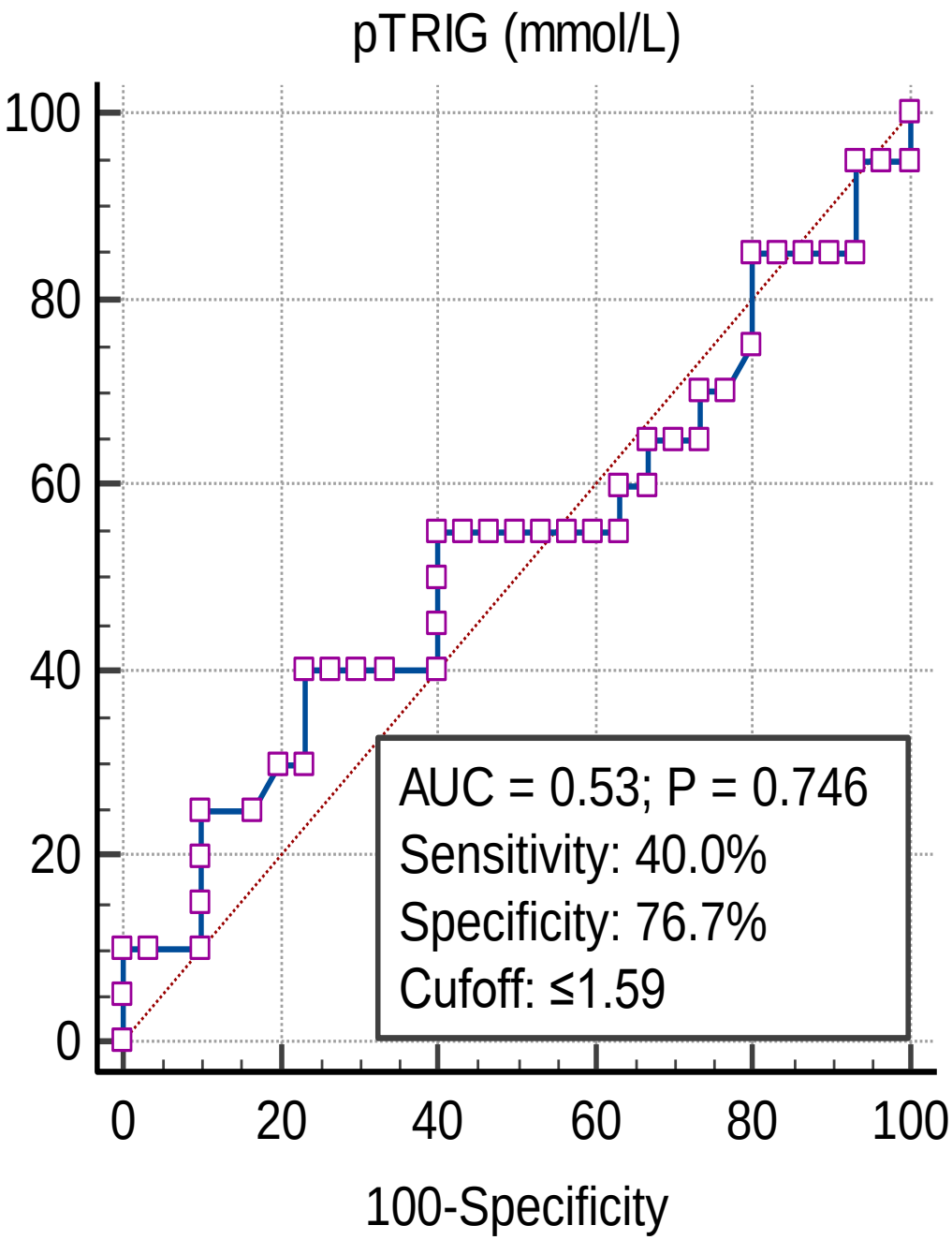

Figure 15: ***The receiver operator characteristic curve shows the predictive ability of placental triglycerides (pTRIG) in the diagnosis of preeclampsia.***

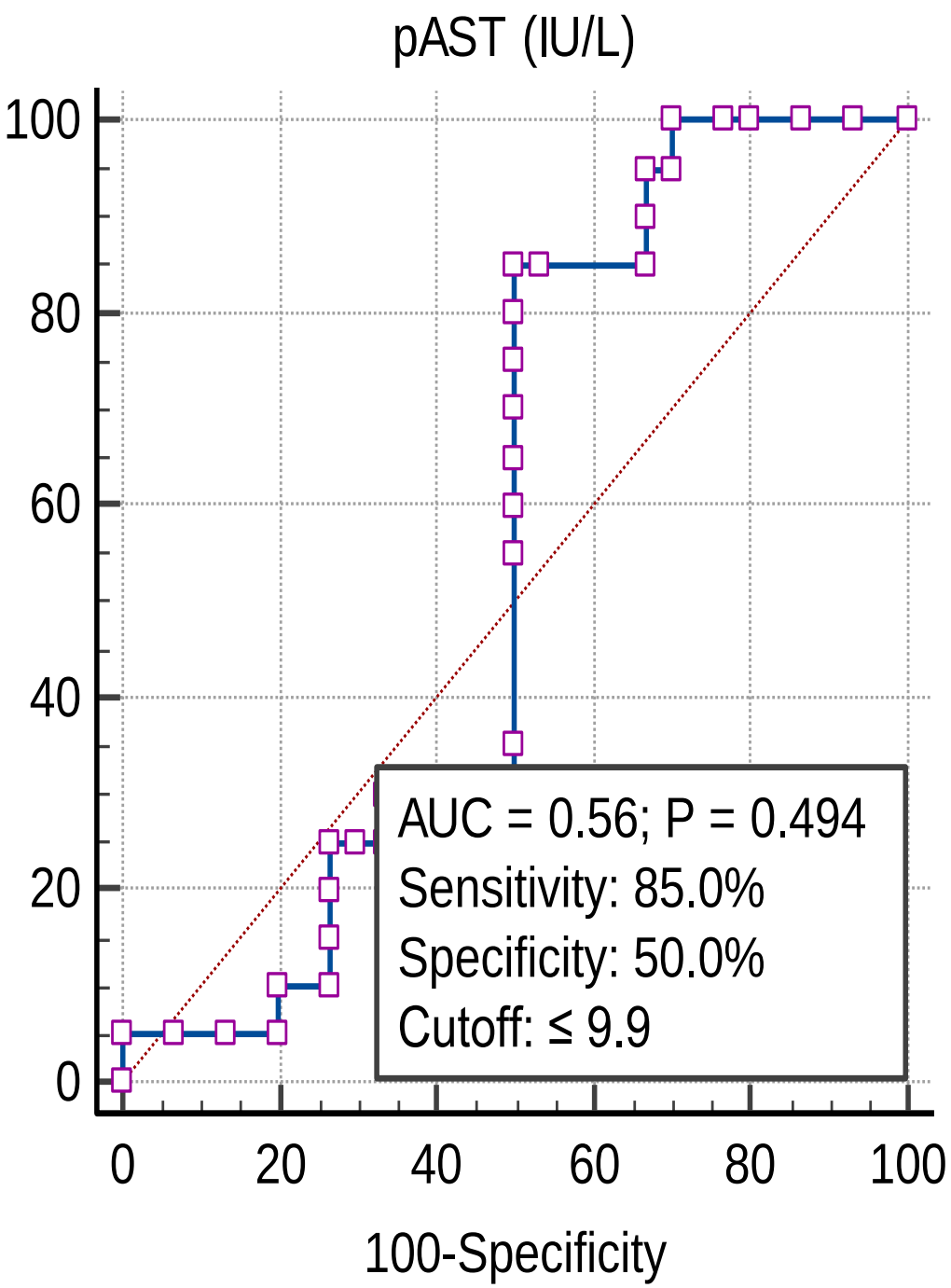

Figure 16: ***The receiver operator characteristic curve shows the predictive ability of placental aspartate aminotransferase (pAST) in the diagnosis of preeclampsia.***

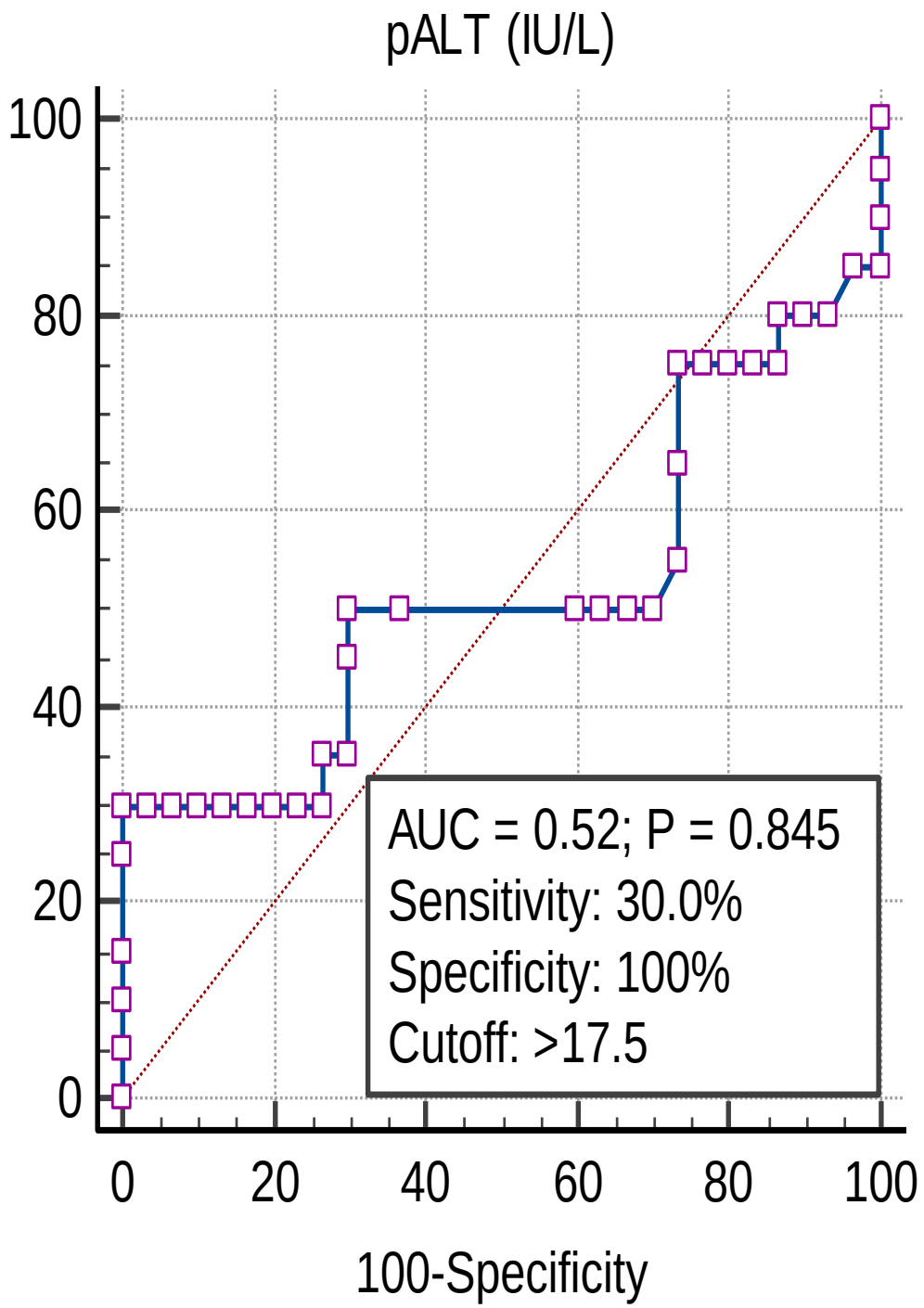

Figure 17: ***The receiver operator characteristic curve shows the predictive ability of placental alanine aminotransferase (pALT) in the diagnosis of preeclampsia.***

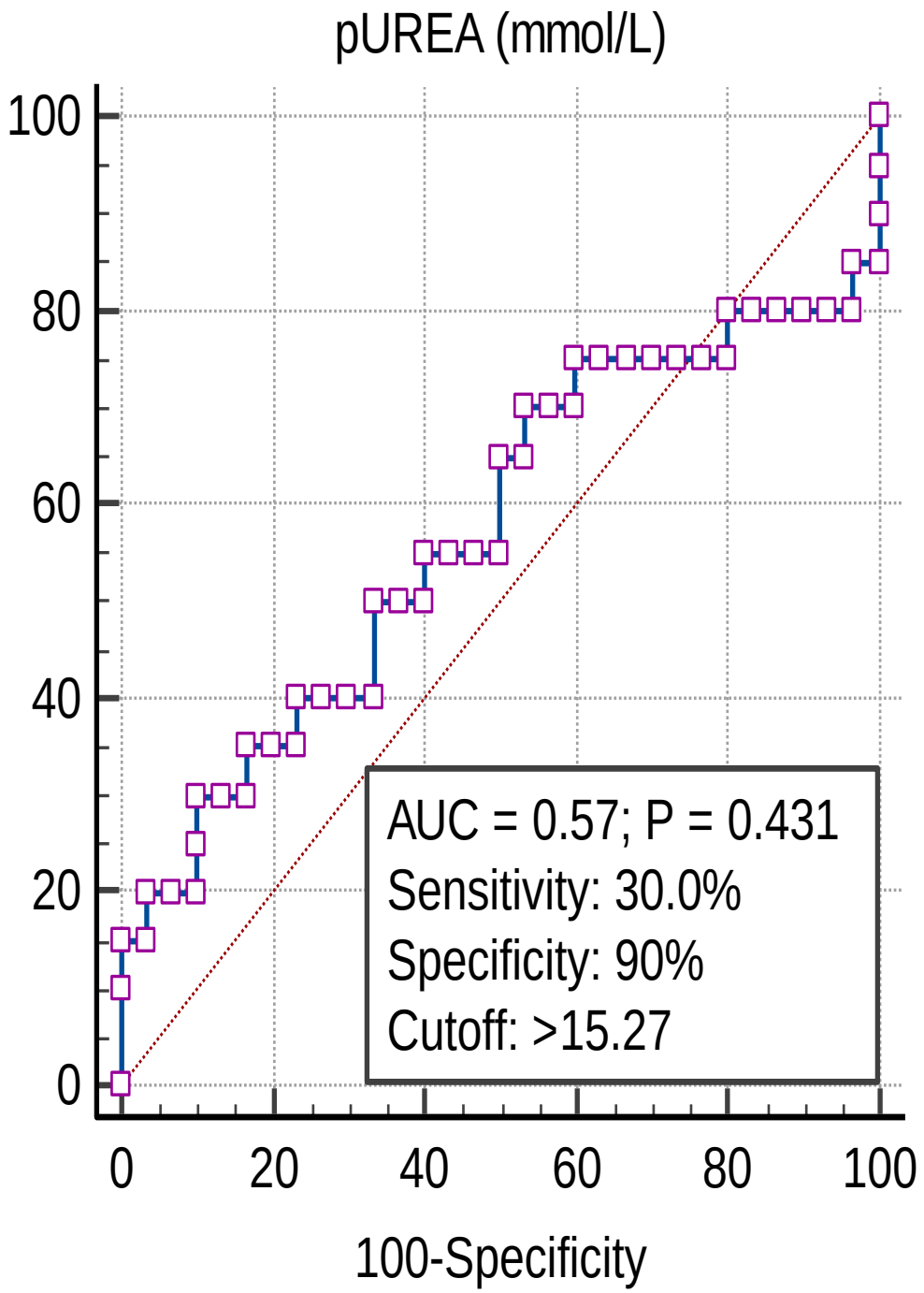

Figure 18: The receiver operator characteristic curve shows the predictive ability of placental urea (pUrea) in the diagnosis of preeclampsia.

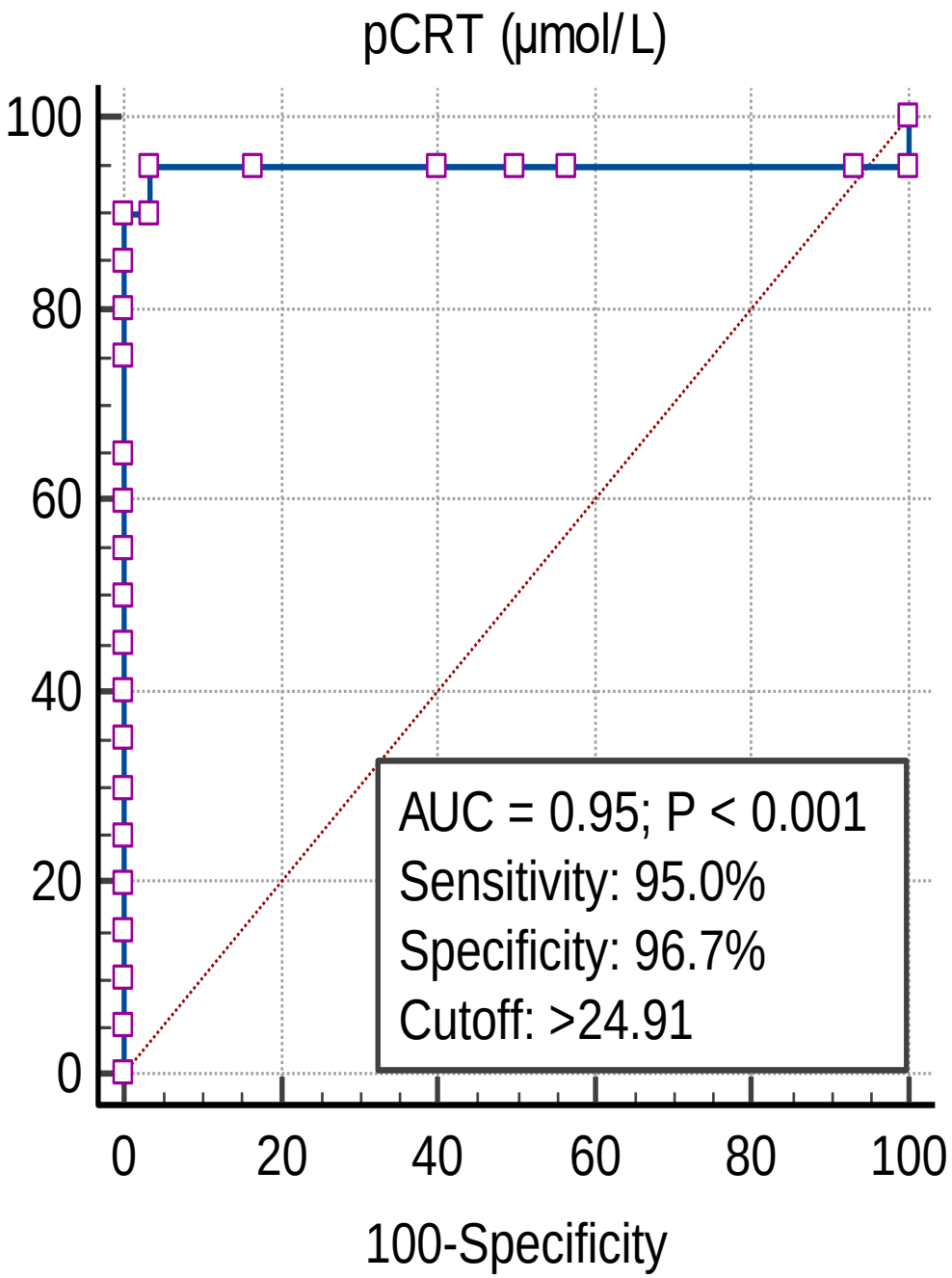

Figure 19: ***The receiver operator characteristic curve shows the predictive ability of placental creatinine (pCRT) in the diagnosis of preeclampsia.***

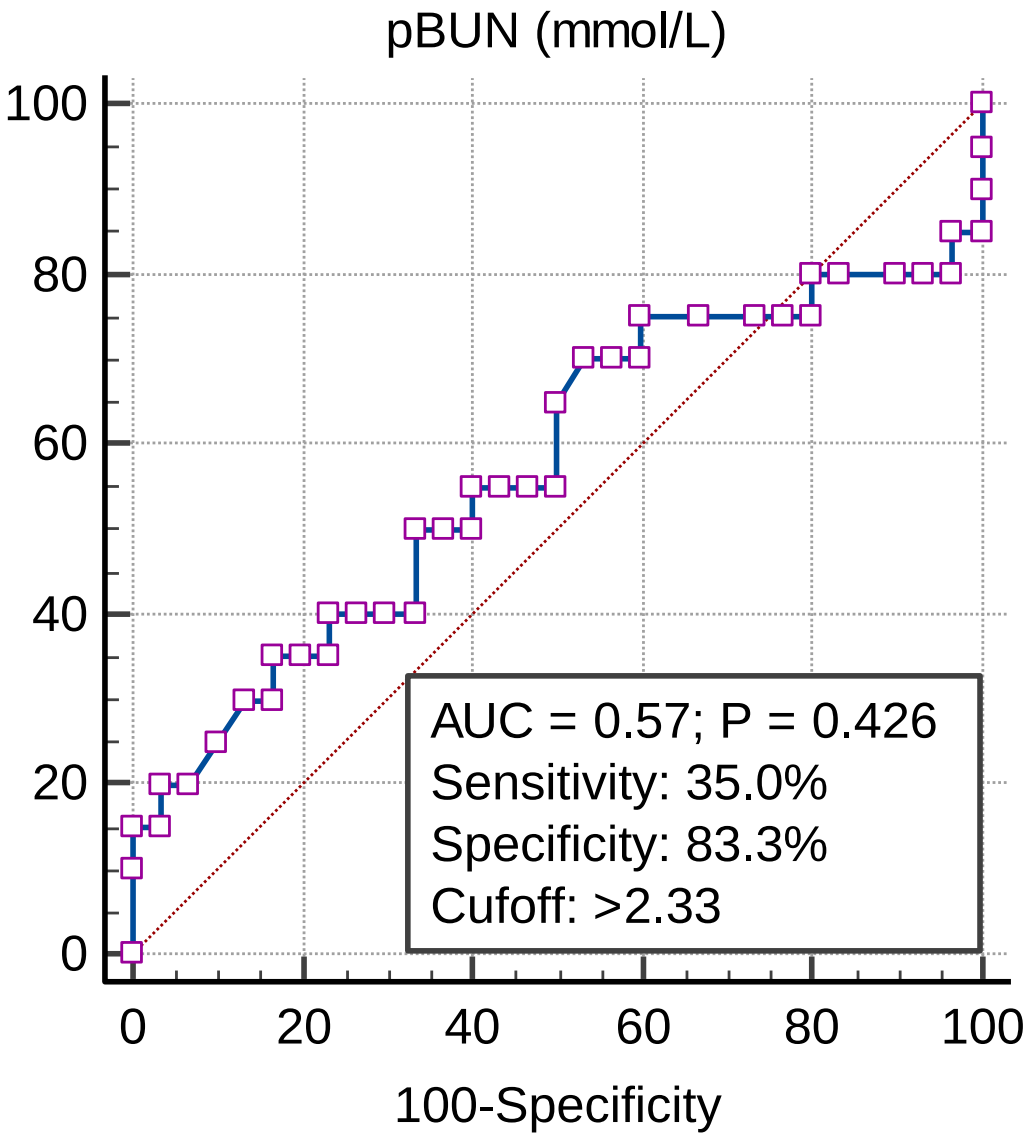

Figure 20: *The receiver operator characteristic curve shows the predictive ability of placental blood urea nitrogen (pBUN) in the diagnosis of preeclampsia*

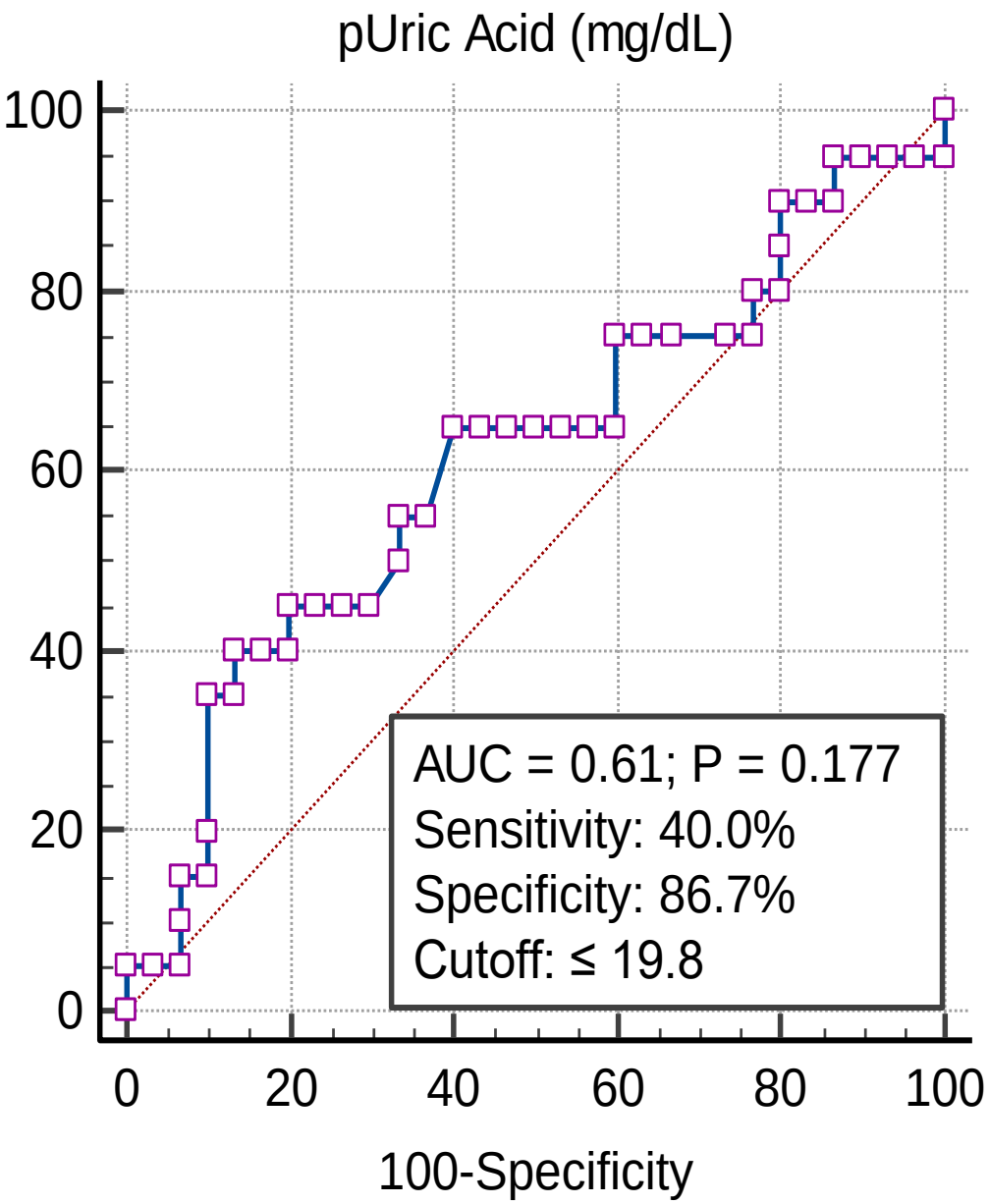

Figure 21: ***The receiver operator characteristic curve shows the predictive ability of placental uric acid in the diagnosis of preeclampsia.***

The predictive accuracies of serum lipids, markers of hepatic and renal functions were determined (Figures 21 - 30). Among the serum lipids, HDL and LDL cholesterol were the only significant variables with the respective area under the curves at 0.68 (P=0.037) and 0.86 (P<0.001). While serum AST and ALT were both predictive of preeclampsia, ALT was better (AUC: 0.93 vs 0.95). Regarding the markers of renal function, all demonstrated significant potential for the prediction of preeclampsia with area under the curve ranging from 0.70 (P=0.007) for eGFR to 0.77 (P<0.001) for creatinine.

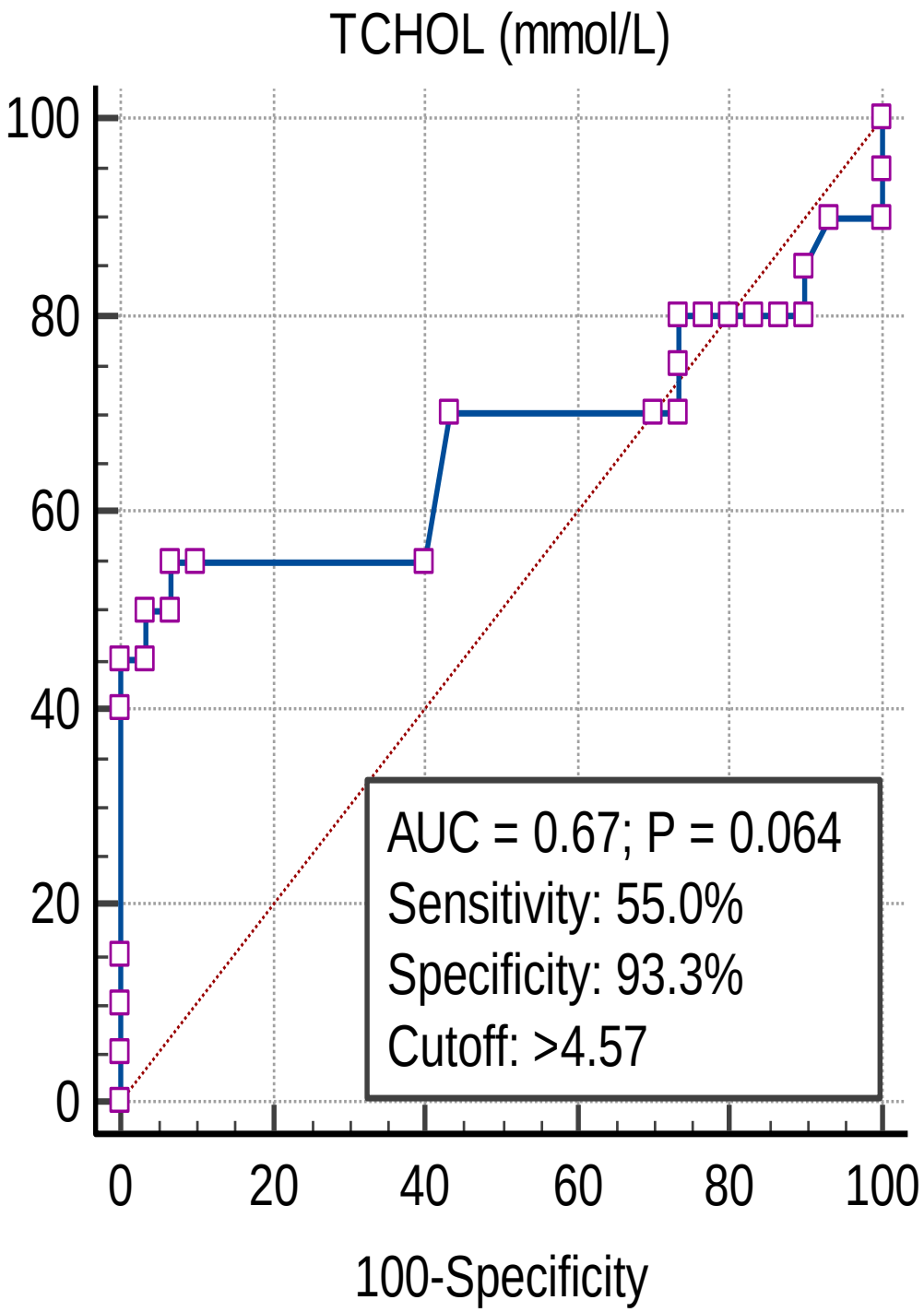

Figure 22: ***The receiver operator characteristic curve shows the predictive ability of serum total cholesterol (TCHOL) in the diagnosis of preeclampsia.***

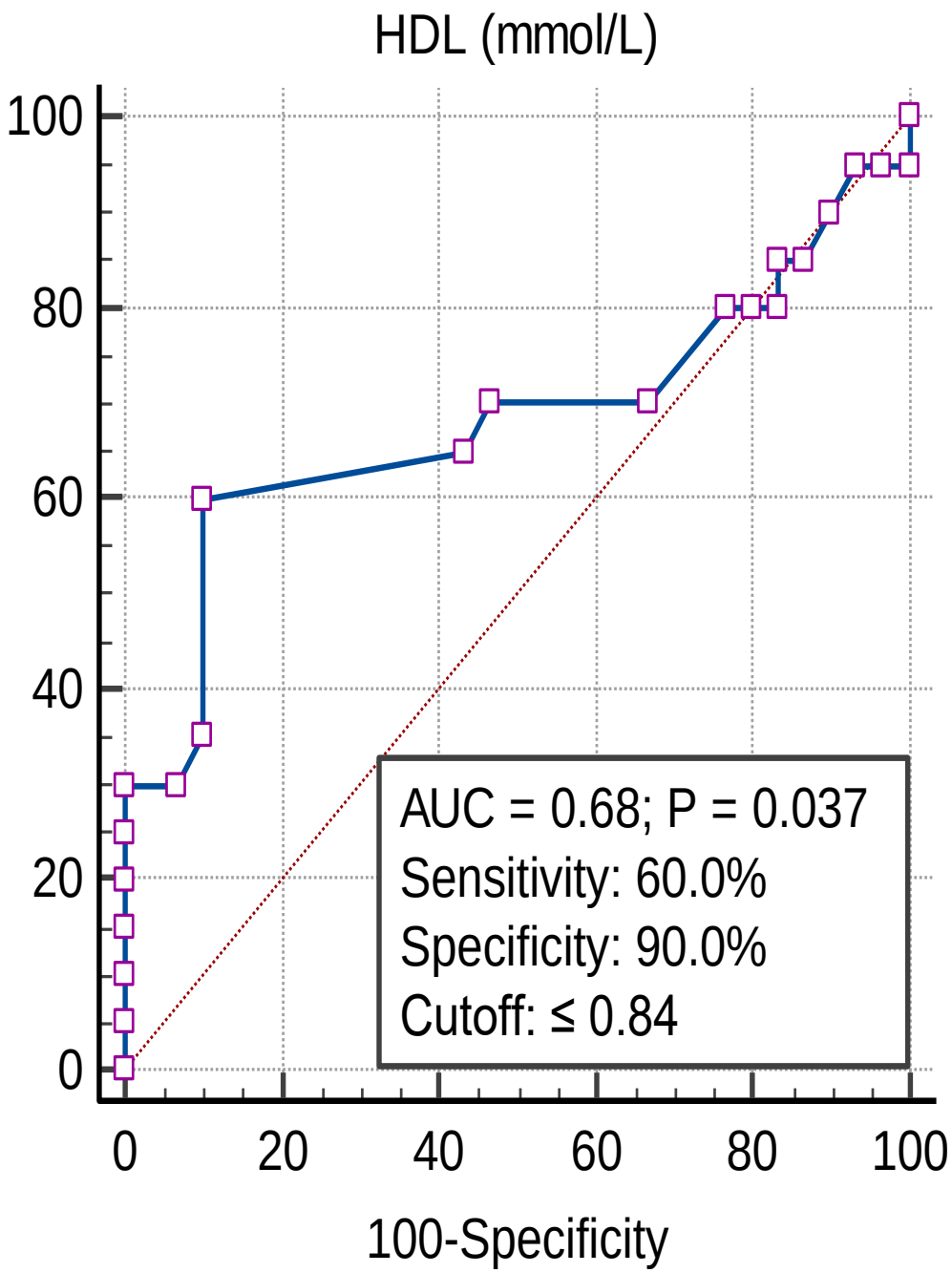

Figure 23: *The receiver operator characteristic curve shows the predictive ability of serum high-density lipoprotein (HDL) cholesterol in the diagnosis of preeclampsia*

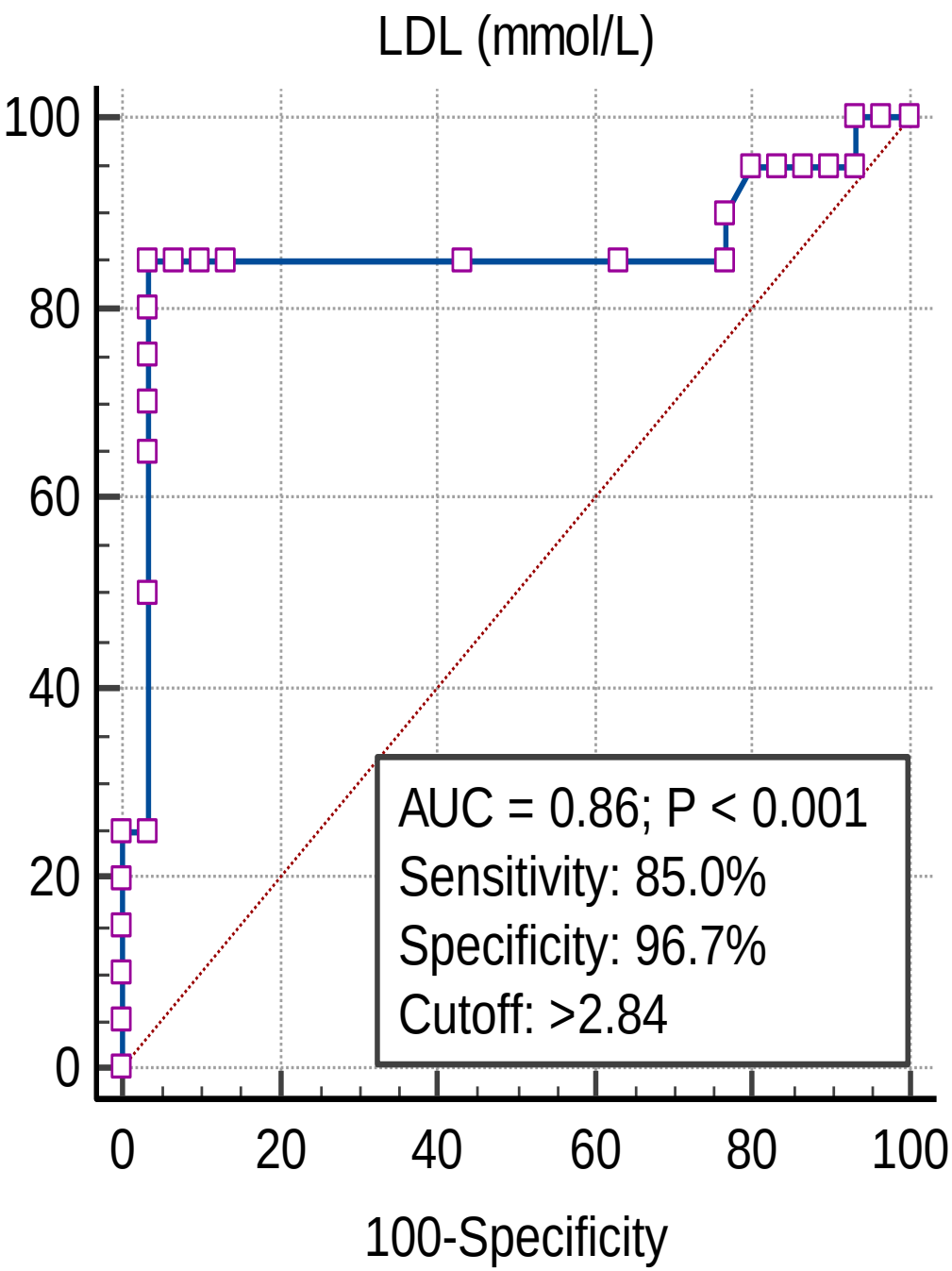

Figure 24: ***The receiver operator characteristic curve shows the predictive ability of serum low density lipoprotein (LDL) cholesterol in the diagnosis of preeclampsia.***

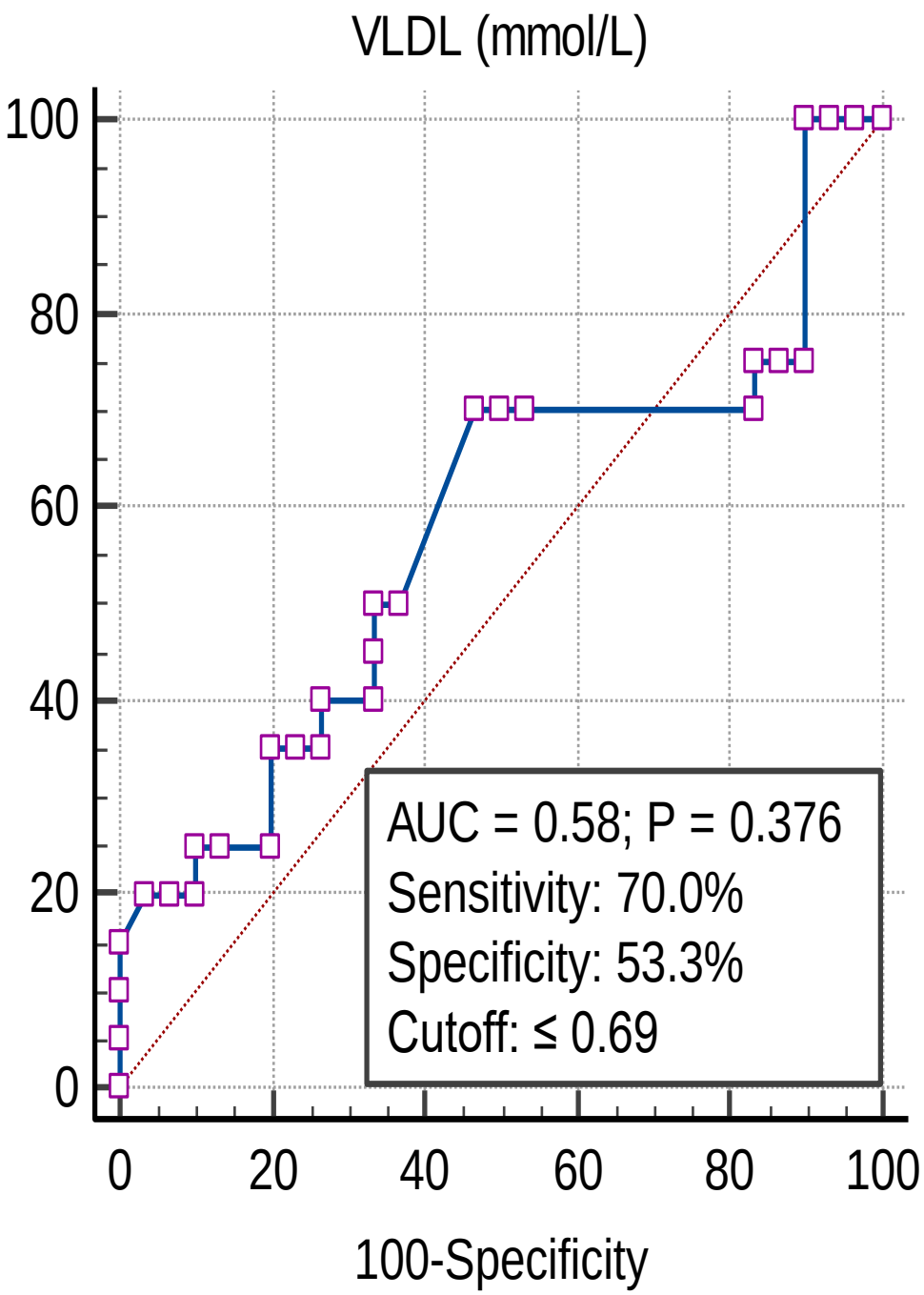

Figure 25: *The receiver operator characteristic curve shows the predictive ability of serum very low-density lipoprotein (VLDL) cholesterol in the diagnosis of preeclampsia.*

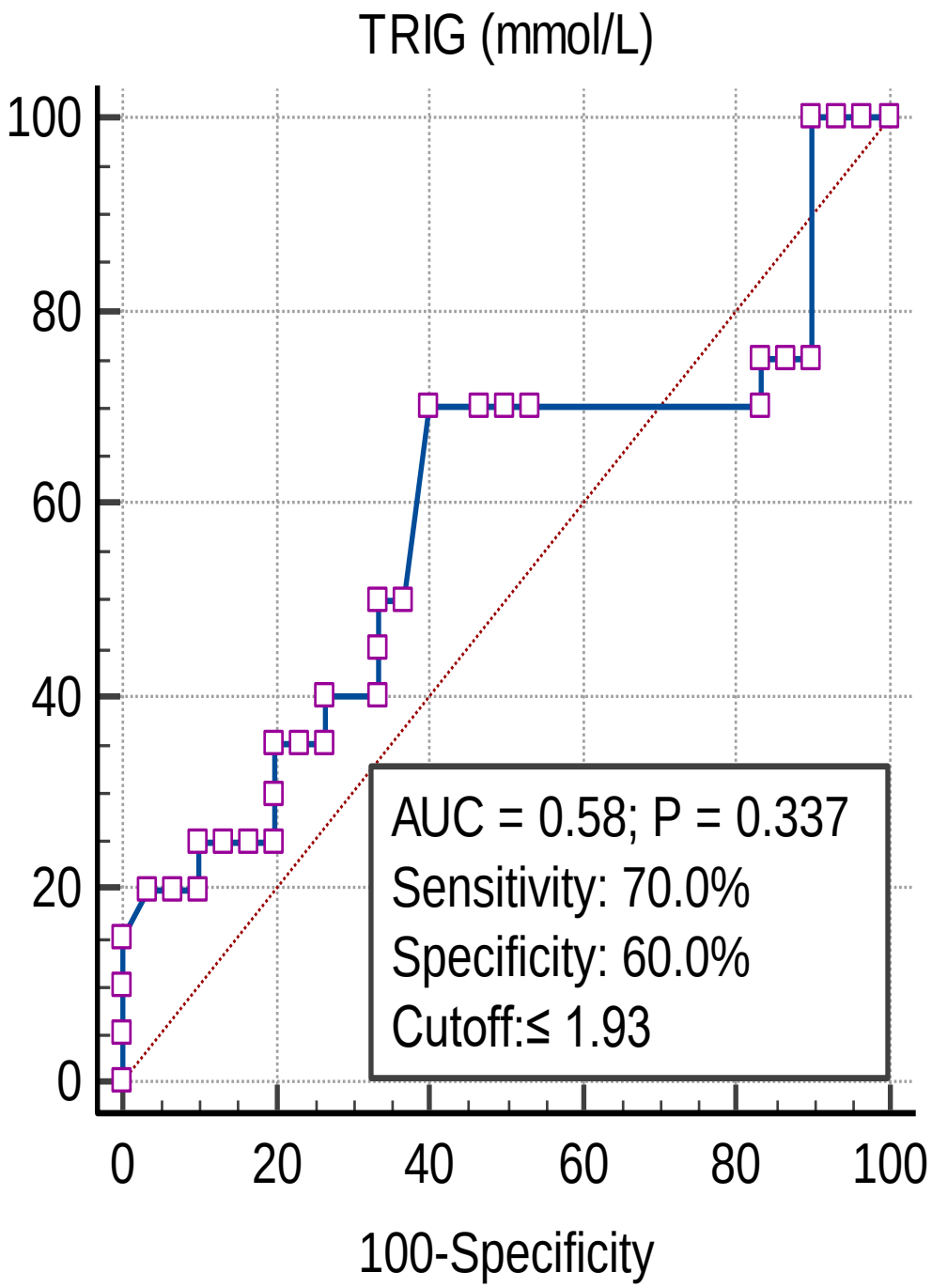

Figure 26: ***The receiver operator characteristic curve shows the predictive ability of serum triglycerides (TRIG) in the diagnosis of preeclampsia.***

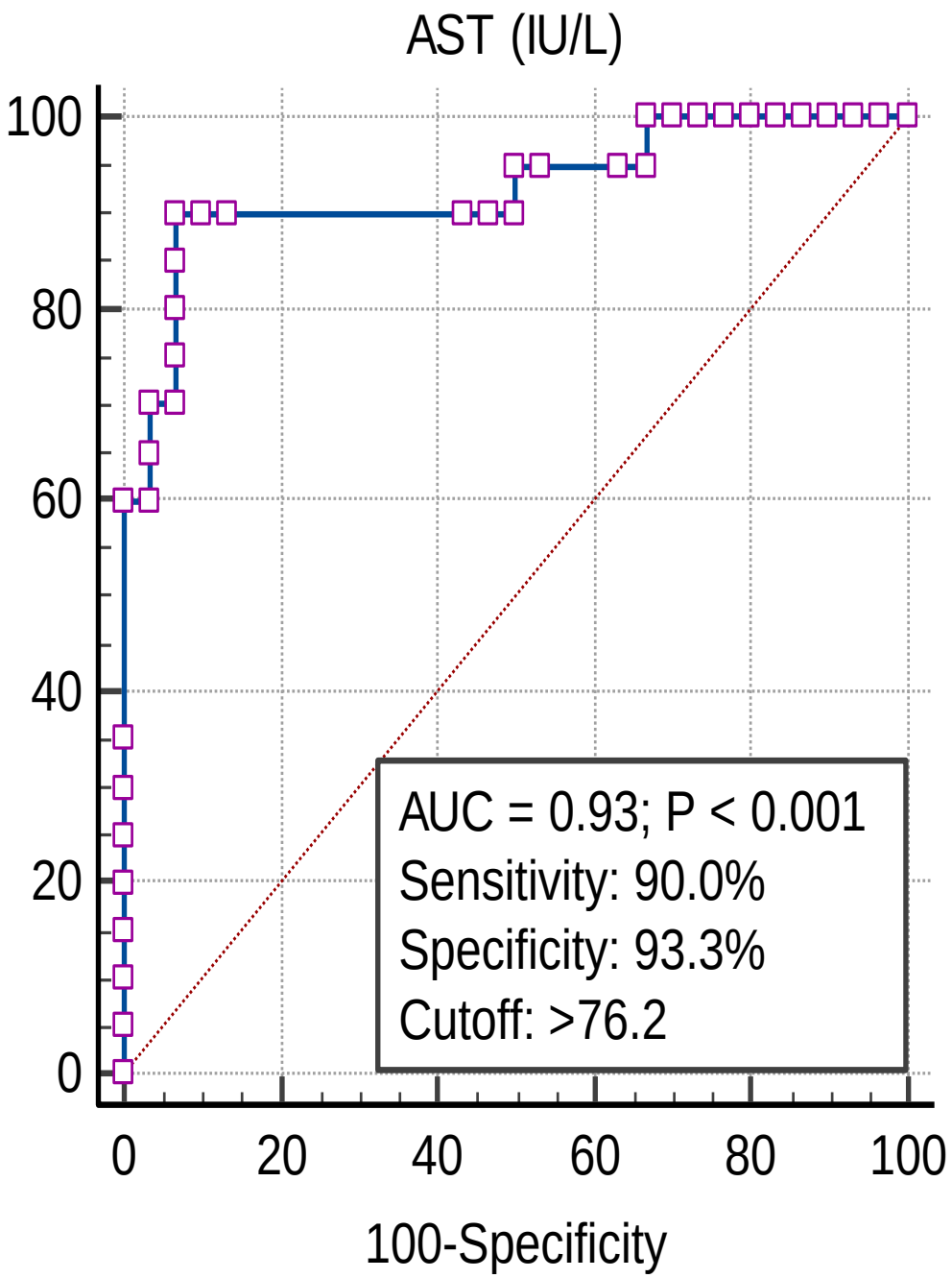

Figure 27: *The receiver operator characteristic curve shows the predictive ability of serum aspartate aminotransferase (AST) in the diagnosis of preeclampsia.*

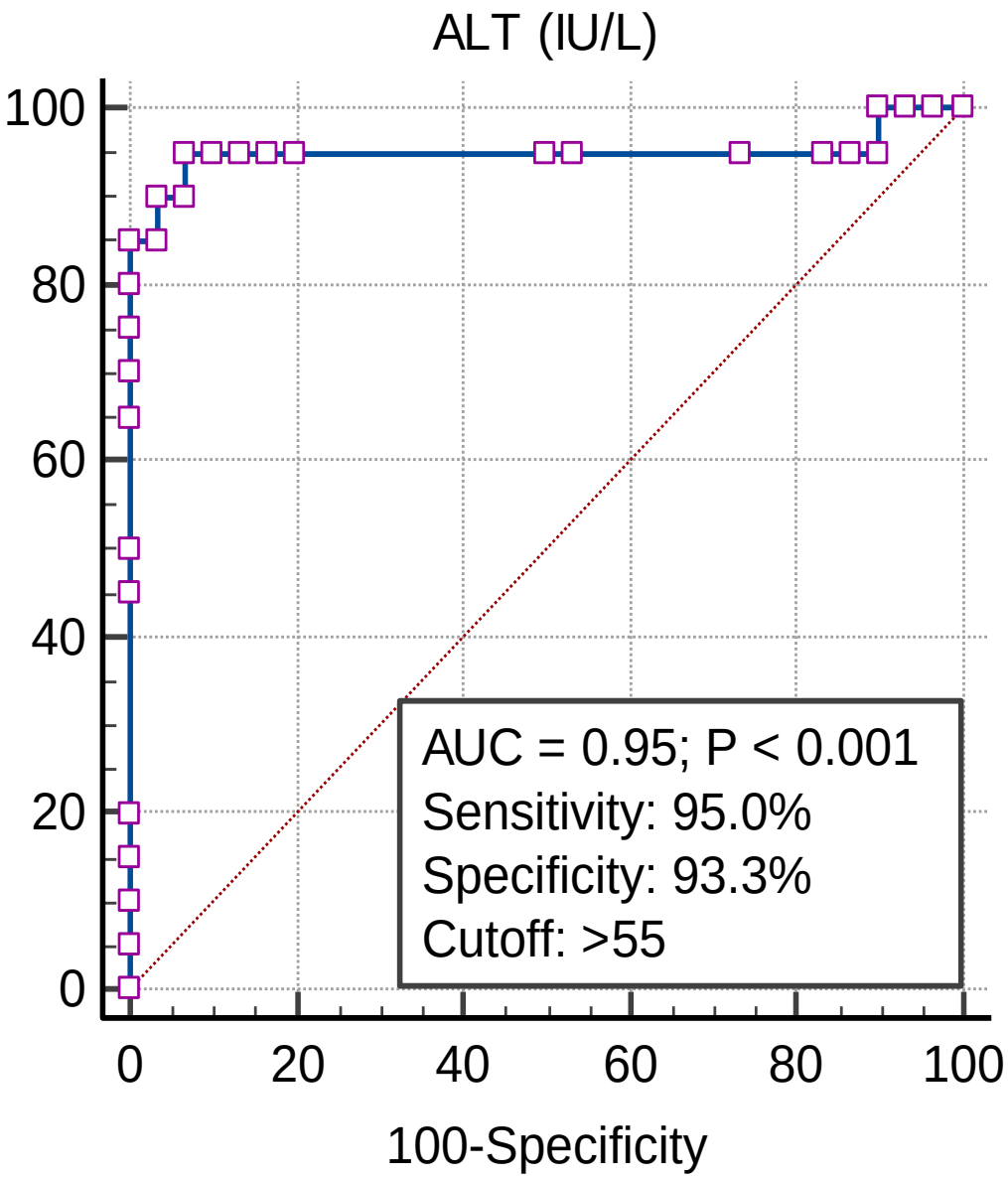

Figure 28: ***The receiver operator characteristic curve shows the predictive ability of serum alanine aminotransferase (ALT) in the diagnosis of preeclampsia.***

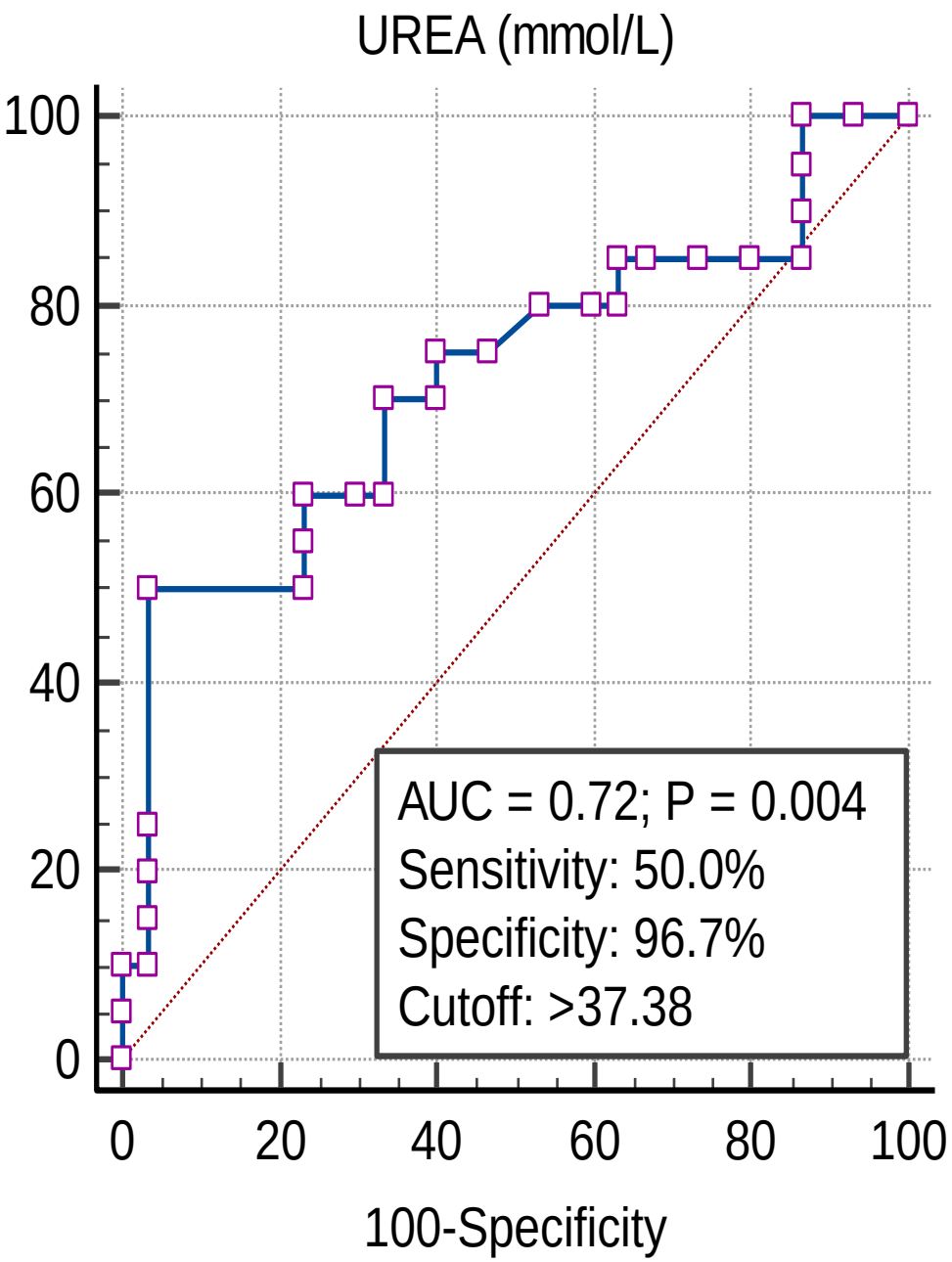

Figure 29: *The receiver operator characteristic curve shows the predictive ability of serum urea in the diagnosis of preeclampsia.*

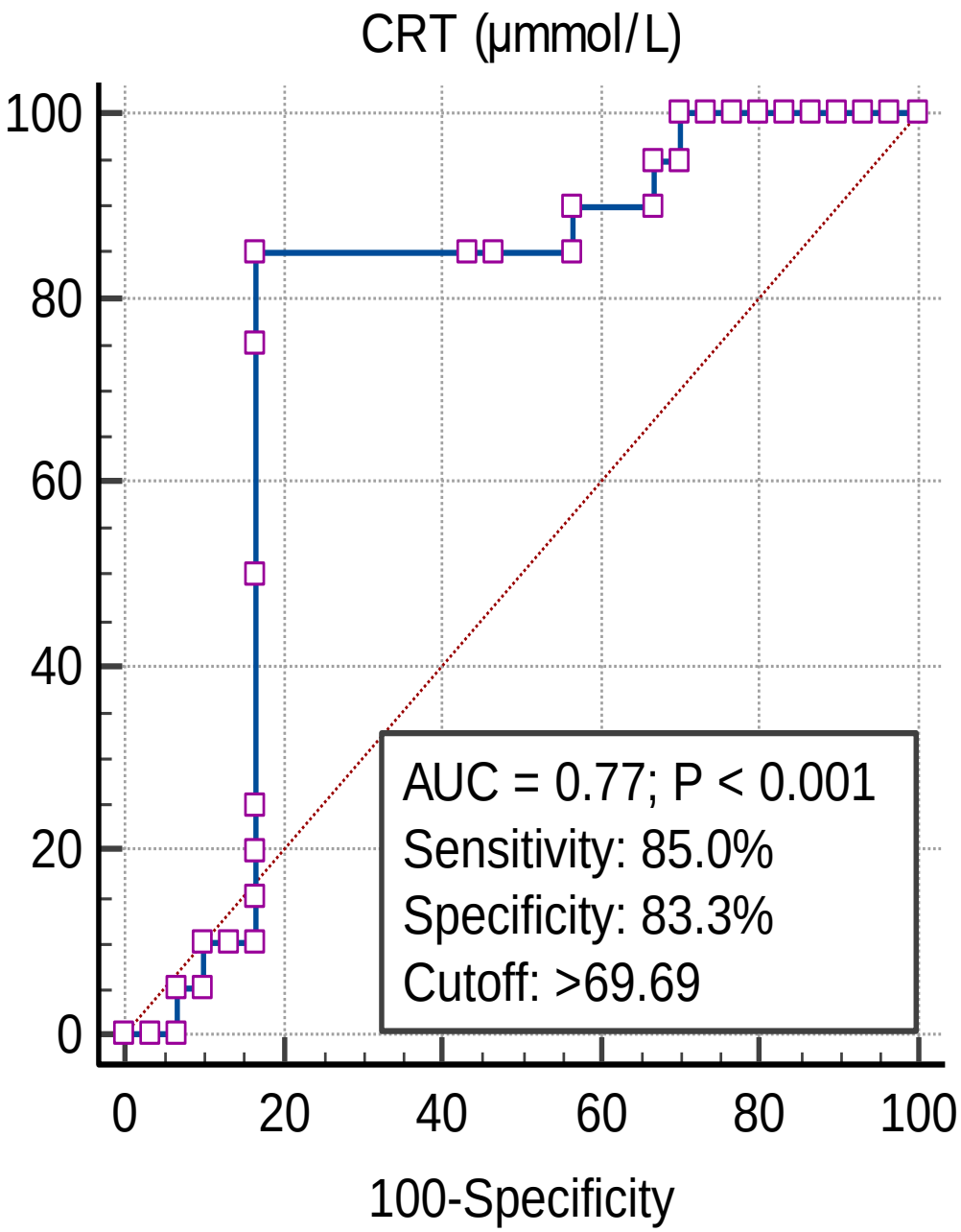

Figure 30: *The receiver operator characteristic curve shows the predictive ability of serum creatinine in the diagnosis of preeclampsia.*

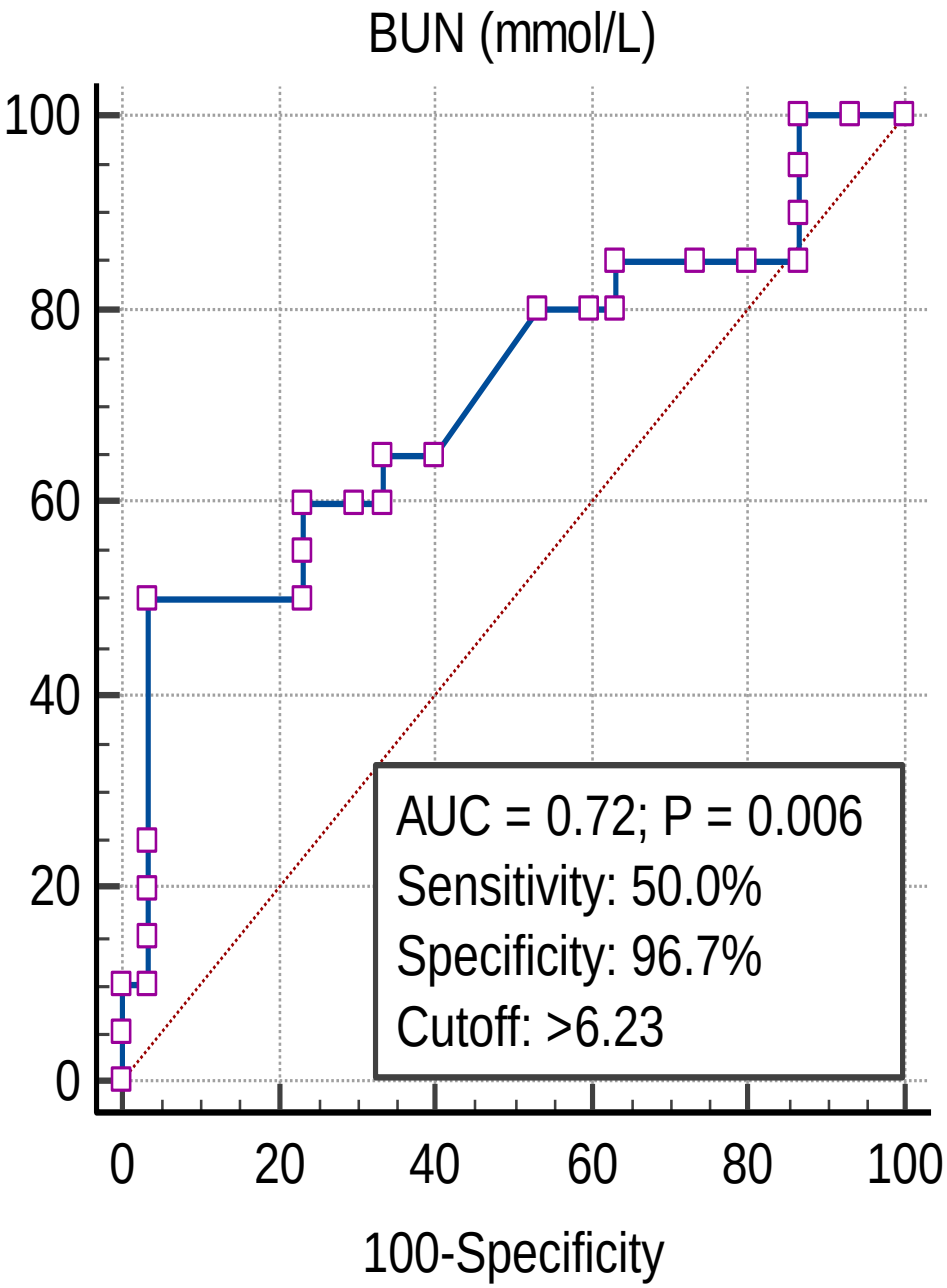

Figure 31: ***The receiver operator characteristic curve shows the predictive ability of serum blood urea nitrogen in the diagnosis of preeclampsia.***

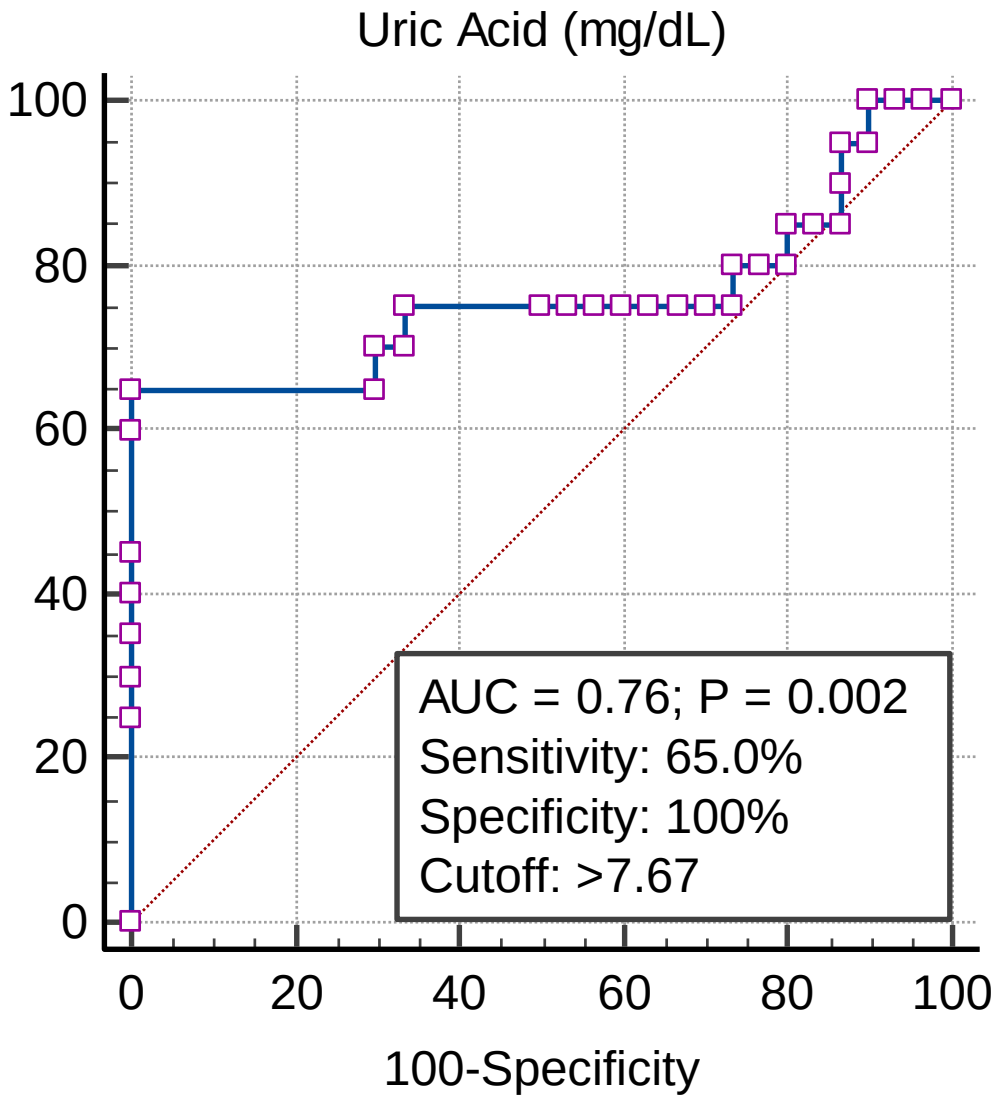

Figure 32*: The receiver operator characteristic curve shows the predictive ability of serum uric acid in the diagnosis of preeclampsia*

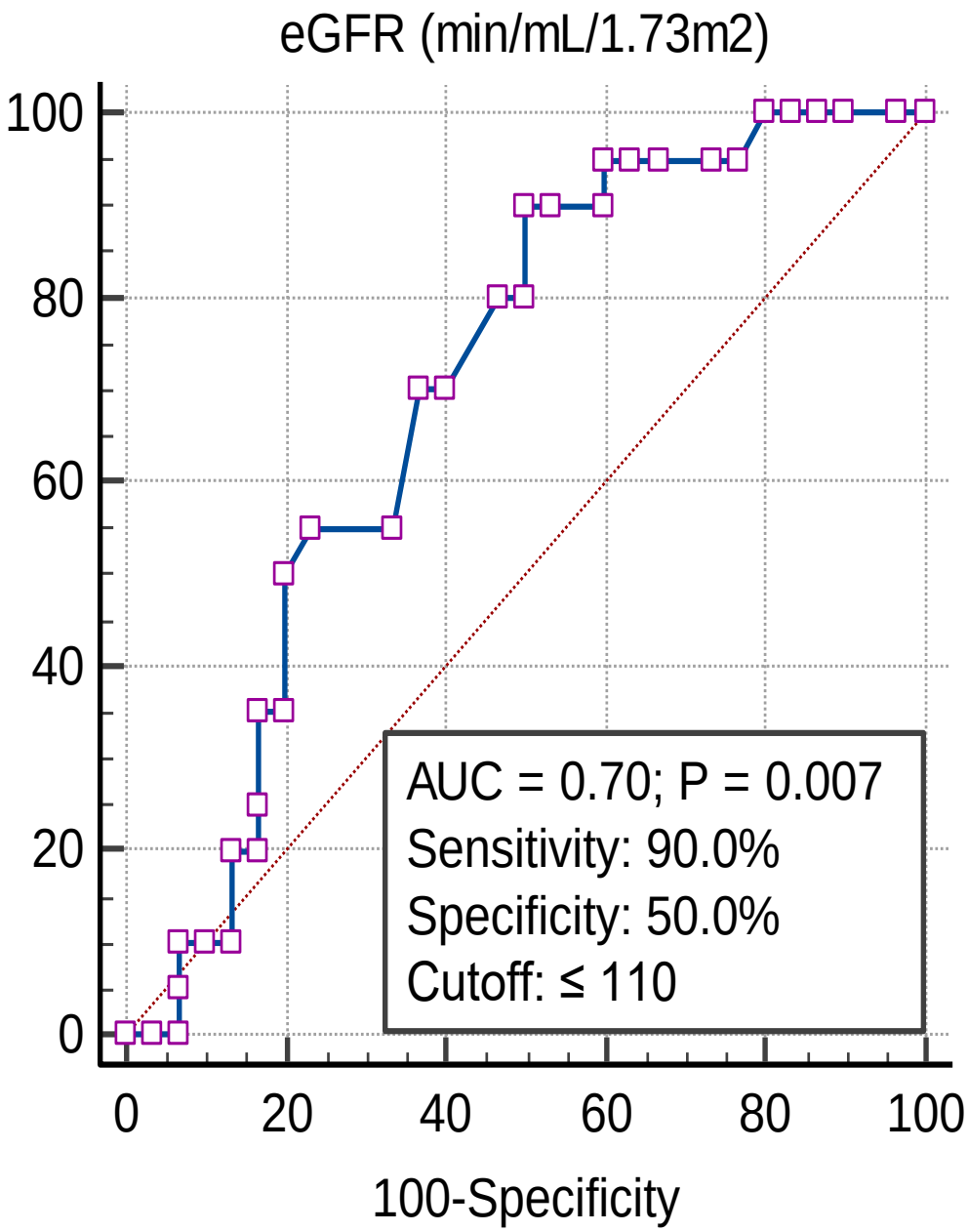

Figure 33: *The receiver operator characteristic curve shows the predictive ability estimated glomerular filtration rate in the diagnosis of preeclampsia*

Table 4. 11: Comparing the predictive accuracies of placental and serum variables for preeclampsia

Variables	Source	Sensitivity	Specificity	AUC	P-value
TCHOL (mmol/L)	Placenta	40.0	90.0	0.58	0.371
	Serum	55.0	93.3	0.67	0.064
HDL (mmol/L)	Placenta	30.0	100	0.53	0.796
	Serum	60.0	90.0	0.68	0.037
LDL (mmol/L)	Placenta	5.0	73.3	0.50	0.976
	Serum	85.0	96.7	0.86	<0.001
VLDL (mmol/L)	Placenta	40.0	76.7	0.54	0.633
	Serum	70.0	53.3	0.58	0.376
TRIG (mmol/L)	Placenta	40.0	76.7	0.53	0.746
	Serum	70.0	50.0	0.68	0.337
AST (IU/L)	Placenta	85.0	50.0	0.56	0.494
	Serum	90.0	93.3	0.93	<0.001
ALT (IU/L)	Placenta	30.0	100	0.52	0.845
	Serum	95.0	93.3	0.95	<0.001
UREA (mmol/L)	Placenta	30.0	90.0	0.57	0.431
	Serum	50.0	96.7	0.72	0.004
CRT (µmol/L)	Placenta	95.0	96.7	0.95	<0.001
	Serum	85.0	73.3	0.77	<0.001
BUN (mmol/L)	Placenta	35.0	83.3	0.57	0.426
	Serum	50.0	96.7	0.72	0.006
UA (mg/dL)	Placenta	40.0	86.7	0.61	0.177
	Serum	65.0	100	0.76	0.002

The results are presented as sensitivity (%), specificity (%), and area under the curve (AUC) with corresponding P-values.

CHAPTER 5

DISCUSSION

5.0 GENERAL INTRODUCTION

The main objective of this research was to investigate the biochemistry markers and oxidative stress indicators present in the placenta and serum, to gain insight into their involvement in the development of preeclampsia. By comparing these markers between preeclamptic and normotensive pregnancies, the study aimed to identify potential predictive markers and elucidate their relationship with preeclampsia. The concentrations of malondialdehyde (MDA) and oxidative stress index (OSI) were markedly elevated in the placentas from preeclamptic pregnancies when compared to those from normotensive pregnancies ($P < 0.001$, $P = 0.048$, $P = 0.001$, and $P < 0.001$, respectively). Conversely, the levels of total antioxidant capacity (TAC) and catalase (CAT) were notably reduced in preeclamptic placentas ($P < 0.001$ and $P = 0.017$, respectively). The study found no significant correlation between the biochemistry variables from the placenta and those from the serum in both normotensive and preeclamptic pregnancies. The receiver operating characteristic (ROC) curve demonstrated that placental Total Peroxide (pTP) has predictive capability in diagnosing preeclampsia. The Neutrophil to Lymphocyte Ratio (NLR) was significantly elevated in pregnancies affected by preeclampsia when compared to those with normotensive pregnancies, indicating an inflammatory response. The Monocyte to Lymphocyte Ratio (MLR) was increased in pregnancies with preeclampsia, indicating it might play a role in the immune response related to the condition. These results improve our understanding of the mechanisms underlying oxidative stress and potential biomarkers linked to preeclampsia, emphasizing the importance of placental biochemistry markers in the early detection and management of this condition.

5.1 ASSOCIATION BETWEEN PREECLAMPSIA AND MATERNAL SOCIODEMOGRAPHIC, ANTHROPOMETRIC, OBSTETRIC AND CLINICAL CHARACTERISTICS

The study's initial objective was to investigate the connection between preeclampsia (PE) and various sociodemographic, obstetric, anthropometric, and clinical characteristics of the participants. The findings, as shown in Table 4.1 and Table 4.2, indicated that PE had significant associations with caesarean or assisted deliveries, preterm births, birth abnormalities, and placental malaria. Furthermore, women with normotensive pregnancies had a much lower BMI than those with PE. These findings are essential for understanding the factors that may impact the development of preeclampsia and the consequences it has on the health of the mother and the baby.

Women with preeclampsia were more prone to having caesarean sections or assisted deliveries, this significantly affects the outcomes for mothers and newborns.

This study examined the connection between preeclampsia and the method of delivery, providing valuable insights into how preeclampsia influences delivery decisions and outcomes.

The study noted a higher frequency of Caesarean sections in preeclamptic pregnancies compared to those with normal blood pressure. This aligns with clinical practices that favour Caesarean delivery when preeclampsia presents risks to the mother or foetus, such as severe hypertension, foetus distress, or stalled labour progress.

These findings underscore the necessity of timely intervention to prevent adverse outcomes.

Although vaginal delivery was achieved in some preeclamptic pregnancies, the success rate was lower compared to normotensive pregnancies. Factors contributing

to successful vaginal deliveries in preeclamptic women included controlled blood pressure, absence of severe foetus distress, and favourable cervical conditions at the onset of labour.

The results for mothers and newborns were strongly correlated with the mode of delivery, Caesarean sections. While often necessary for safety, were associated with increased maternal morbidity, such as infection and longer hospital stays. Neonatal outcomes varied, with preterm births and lower birth weights more common in caesarean deliveries due to preeclampsia, necessitating NICU admissions and intensive neonatal care.

The findings highlight the critical need for individualized delivery plans for women with preeclampsia, considering the condition's severity, the health of the mother and foetus, and the gestational age. To guarantee the best results, a multidisciplinary team comprising obstetricians, specialists in maternal-foetus medicine, and neonatologists should be involved in the decision-making process.

Early detection and meticulous monitoring of preeclamptic symptoms can help in planning the most appropriate timing and mode of delivery. This proactive approach can minimize risks and improve maternal and neonatal outcomes. This finding aligns with several previous research works, suggesting that preeclampsia can cause labour complications, requiring increased medical interventions. (Lambert et al., 2014; Norwitz et al., 2002; Rana et al., 2019; Saadat et al., 2007). The significant consequences of preeclampsia are further highlighted by the elevated rate of premature births and poor birth outcomes in preeclamptic mothers. Preterm deliveries are a serious matter since they are associated with a higher risk of newborn difficulties and long-term health issues for the child. 98% of stillbirths worldwide take place in low-income

nations (LIC) (McClure et al., 2020; McClure et al., 2015), where the stillbirth rates are ten times higher compared to high-income countries (HIC). While the majority of stillbirths in HIC happen before birth, in LIC, most occur at term and during labour or delivery (Cousens *et al.*, 2011). Despite advancements in medical research that have led to improvements in birth outcomes (Goldenberg & Jobe, 2001; Khorrami et al., 2019), these outcomes continue to be significant public health concerns, particularly in low- and middle-income countries, significantly impacting morbidity and mortality during the neonatal, infancy, and early childhood periods (Khorrami et al., 2019).

Numerous studies have identified a range of factors that contribute to low birth weight. For example, a Chinese survey discovered associations between low birth weight and variables; maternal health conditions like gestational diabetes and hypertensive diseases, early mother age, educational attainment, and unfavourable past pregnancy outcomes (Cao et al., 2022). Numerous risk variables, including age, socioeconomic status, gestational diabetes, preeclampsia, and foetal distress, have been linked to preterm delivery (Axame et al., 2022; SHEKHO & YALDA, 2022).

HIV infections and maternal malaria are intimately linked to poor birth outcomes in sub-Saharan Africa. According to research conducted in Nigeria, low birth weight (LBW) affected 14.1% of infants delivered to mothers living with HIV, compared to 1.0% of infants born to mothers living with HIV-negative status (Agboghoroma & Iliyasu, 2015). Parallel to this, a secondary study of a randomised controlled experiment conducted in Malawi discovered that, in contrast to 28.5% of women without malaria, 37.8% of women with malaria gave birth to premature children (van den Broek et al., 2014). Nevertheless, the research revealed no statistically significant distinction between HIV infection and premature delivery (van den Broek et al., 2014). Maternal age's role as a factor in these birth outcomes shows inconsistent results. Some studies

suggest a higher risk of delivering low birth weight babies among teenage mothers compared to older women (Axame et al., 2022; Tshotetsi, 2017), while others indicate that older mothers are more likely to experience these adverse outcomes (El-Gilany & Hammad, 2012; Londero et al., 2019).

In Ghana, the 2014 Ghana Demographic and Health Survey (GDHS) reported a 10% prevalence of low birth weight (LBW) among newborns (GSS, 2014). However, some regions have higher rates, such as 15.2% in the Northern region in 2015 (Abubakari et al., 2015a) and 22.2% in the Ashanti region in 2020 While national data on the prevalence of preterm delivery (PTD) is lacking, studies have identified factors associated with LBW and PTD. For instance, research in the Greater Accra region found that premature rupture of membranes and preeclampsia/eclampsia increased the risk of preterm delivery, whereas attending four or more antenatal care visits reduced this risk (Laar et al., 2010). Additionally, another study on LBW identified associations with anaemia, preterm delivery, education level, and the lack of iron supplements during pregnancy (Symington et al., 2019).

Ghana's Volta Region shows below-average rates of malnutrition indicators such underweight, wasting, and stunting, as well as above-average prenatal care and hospital-based deliveries. However, the area has among of the highest rates of adolescent pregnancy, which is recognised as a risk factor for both preterm delivery and LBW (Axame et al., 2020). It is critical to investigate the variables driving these unfavourable birth outcomes because of the disparity in reported LBW rates and the paucity of research on this topic in the area. The study also revealed a higher frequency of placental malaria among women with preeclampsia. This association is noteworthy as placental malaria is known to have adverse on impact pregnancy outcomes (Chua *et al.*, 2021). Malaria during pregnancy can affect placental function, which can lead to low

birth weight and other problems (Chua *et al.*, 2021; Walther *et al.*, 2010). Understanding the connection between preeclampsia and addressing placental malaria is essential for creating effective strategies to manage and prevent these conditions, particularly in areas where malaria is prevalent, like Ghana. The results did not show significant associations between preeclampsia and sociodemographic factors like parity, gravida, anti-malarial prophylaxis, folic acid, and sickle cell trait. This suggests that preeclampsia is a multifaceted condition affected by various factors in addition to sociodemographic characteristics; (Ayala-Ramírez et al., 2020; Lewandowska et al., 2020; Zhang et al., 2020). However, it is essential to consider that these results might vary in different populations and settings. However, Among pregnant women in Egypt, the risk factors for PE include limited family possessions, poor household sanitation, low parental education, and low economic standing (MOSTAFA et al., 2018). Among pregnant women in Southern Ethiopia the risk factors for PE includes alcohol use, advanced maternal age, a history of hypertension in the family, and DM in the family (Shegaze et al., 2016), whereas in Nairobi, Kenya, a prior history of hypertension, advanced maternal age (35–49 years), employment, and parity (nulliparous or primiparous) are risk factors for preeclampsia (Logan et al., 2020).

The study also found that pregnant women with preeclampsia had a significantly greater BMI than pregnant women with normal blood pressure. This result is in line with previous studies that have often linked obesity to an increased risk of preeclampsia. (He et al., 2020; Lewandowska et al., 2020). High BMI is a modifiable risk factor (Ogunwole et al., 2021; Sohlberg et al., 2012), and therefore promoting healthy weight management before and during pregnancy may help reduce the risk of preeclampsia.

In the study, preeclampsia was linked to a shorter gestational age, which aligns with the clinical characteristics of the condition (Gunnarsdóttir et al., 2019; Hermida et al., 2000). Preterm birth rates are greater in this group of women, most likely due to their lower gestational ages at delivery. This emphasises how crucial it is to treat preeclampsia early on in order to enhance the prognosis for the foetus. The results of this investigation provide important new understandings of the intricate nature of preeclampsia. The significant associations identified between preeclampsia and caesarean delivery, preterm birth, and placental malaria highlight the clinical and public health implications of this condition. The association between preeclampsia and elevated BMI highlights the critical role of weight management in maternal health. These results add to the expanding understanding of preeclampsia, supporting the creation of strategies for its prevention, early detection, and effective management, which can ultimately enhance both maternal and foetus outcomes.

5.2 THE PREDICTIVE ACCURACIES OF BLOOD CELL INDICES FOR PREECLAMPSIA.

The second aim of the study was to evaluate the diagnostic value of white blood cell ratios for preeclampsia. Preeclampsia was marked by an elevated white blood cell count. With the exception of the lymphocyte count, all other white blood cell subpopulations were increased in cases of preeclampsia. It was observed that MLR had a superior diagnostic ability compared to NLR, with a larger AUC.

MLR exhibited higher sensitivity than NLR, while specificities were comparable. Our study indicates that both NLR and MLR may serve as predictive markers for preeclampsia. We have earlier reported similar findings among hypertensive diseases of pregnancy (HDP) in the Ghanaian population (Banyeh et al., 2021). These findings

suggest that alterations in blood cell counts and their ratios could serve as indicators of preeclampsia. Çintesun et al. have proposed that the etiology of preeclampsia may involve allergy-related mechanisms that contribute to its pathogenesis (ÇİNTESUN et al., 2020). According to Kang et al. (Kang *et al*., 2020).

the Neutrophil to Lymphocyte Ratio (NLR) may be a helpful laboratory measure for estimating the severity of preeclampsia and forecasting clinical outcomes. Li et al. have reported their correlation with cervical cancer, despite the fact that this work has emphasised the diagnostic utility of NLR and MLR in preeclampsia (Li et al., 2021). On the other hand, NLR and MLR do not appear to be clinically important in predicting the severity of preeclampsia or the chance of having preeclampsia (PE) and gestational hypertension (GHT) (Ozkan *et al*., 2023). These discrepancies, which do not support the current study's findings, may be attributed to differences in geographical locations or the analytical methods used for blood sample analysis. Additionally, several studies have indicated that NLR serves as a prognostic indicator for pregnancy outcomes, such as miscarriage (Christoforaki et al., 2020), an inflammatory marker in preeclampsia (Thombare et al., 2023) as well as the prediction of preeclampsia in early pregnancies (Gamal El-Din Mahmoud et al., 2021). Our findings align with existing literature that highlights the role of immune system components, such as neutrophils, lymphocytes, and monocytes, in the pathophysiology of preeclampsia. Research has demonstrated that both NLR and MLR have moderate predictive value for hypertensive disorders of pregnancy (HDP) (Wang et al., 2019). Nevertheless, MLR was identified as a superior predictor for HDP compared to NLR. This superiority could stem from the specific contribution of monocytes to the inflammatory response associated with preeclampsia. Monocytes are vital to the immune system, and their increased levels may indicate the systemic inflammation seen in preeclampsia.

The larger Area Under the Curve (AUC) for MLR in the ROC analysis indicates that MLR has a superior ability to differentiate between individuals with and without preeclampsia. A higher AUC signifies a more accurate diagnostic test.

This study has observed that MLR exhibited higher sensitivity than NLR. MLR is more effective at correctly identifying individuals with preeclampsia among those who truly have the condition.

While MLR demonstrated higher sensitivity, specificities between NLR and MLR were reported to be comparable. Comparable specificities suggest that both ratios perform similarly in correctly identifying individuals without preeclampsia among those who truly do not have the condition.

Recent research has indicated that employing basic calculations to derive NLR, MLR, and PLR from regularly performed tests may be an effective means of quickly forecasting unfavourable outcomes in coronavirus-positive pregnant women (Tanacan et al., 2023). NLR and MLR are more useful markers for preeclampsia prognosis, disease severity assessment, and clinical assessment than absolute cell counts. According to a different study, pregnant control patients had considerably lower levels of WBC, neutrophil count, neutrophil percentage, NLR, NMR, and PLR# than patients with preeclampsia ($p < 0.001$) (Liao et al., 2022). Conversely, lymphocyte percentage, monocyte percentage, and PNR exhibited a decrease in PE patients (Çintesun et al., 2018). Moreover, it has been determined that WBC and neutrophil count are separate risk factors for the development of preeclampsia (PE) (Singgih et al., 2021). Furthermore, a number of investigations have demonstrated that the NLR and MLR values in preeclampsia (PE), along with the absolute counts of neutrophils, lymphocytes, and monocytes, differ considerably from those in control groups (Jeon et al., 2017; Wang et al., 2019).

This study shows ROC curves visually demonstrate the discriminatory performance of NLR and MLR, which suggests that elevated white blood cell indices, particularly NLR and MLR, have potential diagnostic value in predicting preeclampsia. The comparison indicated that NLR and MLR outperformed the other indices in predicting preeclampsia. whereas there were similar reports of their utility in pregnancy (Gamal El-Din Mahmoud *et al.*, 2021; Kang *et al*., 2020),

The superior sensitivity of MLR compared to NLR may contribute to its utility as a potential early indicator of preeclampsia, allowing for timely intervention and management. Further studies could explore the utility of these white blood cell indices in larger and diverse populations to investigate the potential of these markers in combination with other clinical parameters for improved predictive accuracy. Both NLR and MLR are potential predictors of preeclampsia, but MLR appears to have a superior diagnostic ability, higher sensitivity, and comparable specificity when compared to NLR. These findings contribute to the exploration of novel biomarkers for the early detection and management of preeclampsia, emphasizing the importance of immune system components in its pathogenesis.

5.3 THE EFFECT OF BLOOD PRESSURE ON THE LEVELS OF PLACENTAL OXIDATIVE STRESS MARKERS

The results of the third objective of the study shed light on the connection between markers of placental oxidative stress and blood pressure. The study reveals that blood pressure significantly influences most placental oxidative stress markers, except for placental total peroxide levels. This implies that variations in placental oxidative stress indicators are linked to variations in blood pressure. Analysis was done on the

combined impact of systolic and diastolic blood pressure, showing that this combination could explain variations in placental oxidative stress markers ranging from 8.3% to 65.3%. The adjusted R-squared values, indicating the model's fit to the data, range from 0.083 to 0.653, reflecting moderate to strong explanatory power. Numerous studies have consistently associated oxidative stress with blood pressure in pregnant women experiencing hypertensive disorders, suggesting that placental oxidative stress may play a critical role in the development and severity of these condition (Ferreira et al., 2009; Phoswa & Khaliq, 2021; Webster et al., 2018).

Hypertension, characterized by elevated blood pressure, can cause endothelial dysfunction, impairing the function of the endothelial cells lining blood vessels (Verma et al., 2019). When blood pressure is elevated, these endothelial cells become less efficient at producing nitric oxide, a crucial vasodilator essential for maintaining vascular health (Konukoglu & Kurtulus, 2016; Zhao et al., 2015). This dysfunction leads to vasoconstriction, reducing blood flow and oxygen supply to the placenta. The reduced nitric oxide levels create an imbalance between vasoconstrictive and vasodilatory factors (Konukoglu & Uzun, 2017; Zhao et al., 2015). This imbalance can lead to the generation of reactive oxygen species (ROS), which contribute to oxidative stress by damaging cellular structures (Oyinloye et al., 2015; Zhou et al., 2015). This series of events may account for the positive connection between placental malondialdehyde (MDA) and total antioxidant capacity (TAC), markers of oxidative stress, and systolic and diastolic blood pressure (DBP) found in the current study.

The tendency for hypertension to cause placental ischaemia, which is characterised by a transient decrease in blood flow to the placenta as a result of uterine blood arteries becoming constricted (Aouache et al., 2018), may represent a contributory factor to the findings in the current study. This is particularly relevant as ischaemia is often followed

by reperfusion when blood flow is restored, leading to placental cells being exposed to ischaemia-reperfusion events (Aouache et al., 2018). This exposure, in turn, gives rise to the production of ROS as a byproduct, subsequently causing DNA, protein, and lipid peroxidation in placental cells. The present study findings is in agreement with that of Verma et al., (2019) which found a strong association between MDA and hypertension. Furthermore, ROS generated during hypertension-induced oxidative stress can directly inflict damage upon DNA. ROS can oxidize DNA bases, leading to the formation of DNA lesions (Ranchoux et al., 2016). Such oxidative DNA damage may ultimately result in mutations or errors during DNA replication, potentially jeopardizing the integrity of placental DNA (Ranchoux et al., 2016).

The findings from this study indicate a correlation between blood pressure variations and alterations in oxidative stress markers within the placenta. This association highlights the intricate interplay between hypertensive disorders, particularly blood pressure variations, and One phenomenon that plays a role in the pathophysiology of several pregnancy-related problems is oxidative stress. The combined effect of blood pressure's diastolic and systolic phases highlights the significance of considering both components of blood pressure in understanding their impact on oxidative stress within the placenta. Total Antioxidant Capacity (TAC) was the most impacted, with high adjusted R-squared values (0.652-0.653).

Malondialdehyde (MDA) was the least impacted, with a lower adjusted R-squared value (0.083).

The data highlights that TAC, representing the overall antioxidant defense, is the most impacted by variations in blood pressure. High adjusted R-squared values (0.652-0.653) suggest that a significant proportion of the variability in TAC levels can be attributed to changes in blood pressure's diastolic and systolic levels. Conversely, MDA, which

indicates lipid peroxidation and oxidative stress, is the least impacted, with a lower adjusted R-squared value (0.083). This implies that variations in blood pressure contribute less to the observed variability in MDA levels.

The study emphasizes that, in comparison to diastolic blood pressure, systolic blood pressure has a more notable impact on indicators of placental oxidative stress. This discovery emphasizes how the components of systolic and diastolic blood pressure have different functions when it comes to oxidative stress in the placenta. Studies have demonstrated how placental oxidative stress is impacted by mean arterial blood pressure (Kuc et al., 2013). Systolic blood pressure appears to be a more significant element in the equations and regression analyses, which reflect the influence of systolic blood pressure seen in this study. Research indicates that the sensitivity for early prediction of preeclampsia in pregnancy with an elevated blood pressure measurement (130 to 85 mm Hg) varies between 16% and 57%, while specificity ranges from 75% to 98% (Moutquin et al., 1985). Different oxidative stress markers show varying degrees of responsiveness to changes in blood pressure.

Our study emphasizes that systolic blood pressure has a more substantial impact on placental oxidative stress markers compared to diastolic blood pressure.

In a related study, an elevated systolic blood pressure (sBP) markedly raised the occurrence of early-onset superimposed preeclampsia (Kuc et al., 2013).

Research findings indicate that severe systolic hypertension, as opposed to severe diastolic hypertension, is the predominant factor leading to stroke development in individuals with severe preeclampsia and eclampsia (Martin Jr et al., 2005). Therefore, a shift in perspective is necessary, suggesting the consideration of antihypertensive therapy for individuals with severe preeclampsia and eclampsia who exhibit elevated values of systolic blood pressure. Including diastolic blood pressure in the multivariable

analysis along with systolic blood pressure did not significantly affect the levels of placental oxidative stress markers. Interestingly, blood pressure did not significantly impact placental total peroxide levels, suggesting that other factors or mechanisms may be influencing this specific oxidative stress marker.

The note about TAC being a calculated variable and potentially influenced by the additive effect from other variables highlights the complexity of interpreting TAC levels. This underscores the importance of considering interactions between different variables when assessing the impact on oxidative stress markers.

P-values below 0.05 for most equations indicate that the relationships observed are statistically significant, adding confidence to the findings. Ozturk et al. found a strong correlation between the levels of Total Oxidant Status (TOS) and Total Antioxidant Status (TAS) in both cord and maternal plasma in women with preeclampsia as compared to control group (Kalaycı et al., 2011). Similarly, Mert et al. reported that women with preeclampsia and intrauterine growth restriction had higher TOS and TAS levels compared to women with healthy pregnancies (Mert et al., 2012). Additionally, Fenzl et al. discovered that total antioxidant capacity (TAC) and TOS were significantly elevated in the serum of preeclamptic pregnant women (Fenzl et al., 2013). While the raised TAC in early-stage preeclampsia may represent a preventive response against this stress, the increased TOS in all pregnant women implies that there was underlying oxidative damage during pregnancy.

The current study offers valuable insights into how blood pressure affects placental oxidative stress markers, revealing different impacts on specific markers. By focusing on systolic blood pressure and examining the nuanced effects on various oxidative stress markers, the study improves our understanding of the intricate interactions between blood pressure and placental health during pregnancy. The data highlights the

intricate relationship between blood pressure variations and placental oxidative stress markers, with a particular emphasis on how systolic and diastolic blood pressure differentially affect TAC and MDA.

These findings enhance our understanding of how blood pressure variations might affect oxidative stress, providing potential mechanisms involved in hypertensive disorders during pregnancy.

5.4 THE PREDICTIVE ACCURACIES OF PLACENTAL OXIDATIVE STRESS MARKERS FOR PREECLAMPSIA

The fourth objective of the study was to assess how accurately placental oxidative stress markers can predict preeclampsia. The study found notable differences in the placental levels of MDA, TAC, CAT, and OSI between pregnancies affected by preeclampsia and those with normal blood pressure. Similarly, TAC and OSI were used in assessing preeclampsia from a population of pregnant women (Yiyenoğlu et al., 2014). The results suggest a noteworthy distinction in placental oxidative stress markers between normotensive pregnancies and preeclampsia.

Placental levels of creatinine, MDA, TAC, CAT, and TP demonstrated significant predictive potential in diagnosing preeclampsia

Elevated levels of Malondialdehyde (MDA) and Oxidative Stress Index (OSI) in preeclampsia indicate increased oxidative stress. MDA, a marker of lipid peroxidation, suggests heightened oxidative damage to lipids. OSI, derived from multiple oxidative stress markers, offers a holistic assessment of oxidative stress levels. Reduced Total Antioxidant Capacity (TAC) and Catalase (CAT) levels in preeclampsia imply weakened antioxidant defense mechanisms. TAC measures the overall capability of biological samples to combat oxidative stress, with lower levels indicating a diminished

ability to neutralize reactive oxygen species. CAT is a crucial antioxidant enzyme, and diminished activity implies a weakened ability to detoxify hydrogen peroxide. Placental levels of creatinine, MDA, TAC, CAT, and Total Peroxide (TP) exhibit significant predictive potential in diagnosing preeclampsia. These biomarkers collectively provide insights into the oxidative stress status, antioxidant defense capacity, and overall placental function in the context of preeclampsia. This study has shown that Placental catalase activity (pCAT) emerges as the most predictive variable for diagnosing preeclampsia. When full sensitivity and specificity are combined with an ideal Area Under the Curve (AUC), demonstrates that pCAT is highly effective in differentiating between preeclampsia and non-preeclamptic conditions. This indicates that catalase activity in the placenta is crucial for predicting and diagnosing preeclampsia. Our study shows that CAT is the sole antioxidant linked to the severity of the disease, indicating its potential as a valuable predictor for preeclampsia. O^{-2} holds significant biological relevance as a free radical. It comes from the reduction of oxygen by one electron and is a potent weapon that the immune system uses to fight off invasive invaders. The primary enzyme responsible for neutralizing O^{-2} and transforming it into H_2O_2 and water is superoxide dismutase (SOD). Then, H_2O_2 is swiftly neutralized by catalase (CAT). On the other hand, pathological states like preeclampsia can also cause O^{-2} to be produced. Hydrogen peroxide (H_2O_2) and other reactive oxygen species (ROS) are essential to many physiological and pathological processes in the body (Sies & Jones, 2020). These extremely reactive compounds are implicated in immunological responses, signalling pathways, and cellular control. On the other hand, an overabundance of ROS can cause oxidative stress, which can harm cellular constituents like DNA, lipids, and proteins (Li et al., 2017). On the other hand, an overabundance of

ROS can cause oxidative stress, which can harm cellular constituents like DNA, lipids, and proteins.

A study has indicated that catalase (CAT) may be the sole antioxidant associated with the severity of the condition, suggesting its potential as a promising predictor for preeclampsia (PE) (Ahmad et al., 2019). One essential enzyme that is present in all cells is called catalase. Catalase act as a potent antioxidant, reducing the harmful effects of reactive oxygen species (ROS) in the body tissues.

In particular, it makes hydrogen peroxide easier to convert into water and oxygen (Deisseroth & Dounce, 1970), thereby reducing the potential damage from this reactive molecule. By breaking down hydrogen peroxide, catalase aids in preserving cellular homeostasis and shielding cells from oxidative stress. Maintaining the delicate equilibrium between ROS and antioxidants such as catalase is essential for cellular health. While ROS serve important functions in various cellular processes, an excess of these molecules can lead to oxidative damage. Catalase, by efficiently breaking down hydrogen peroxide, contributes to the overall antioxidant defense system, emphasizing its importance in safeguarding cells and regulating redox balance. The ROC curves visually represent the trade-off between sensitivity and specificity, with each curve illustrating the diagnostic accuracy of the respective placental biochemistry variable.

Research findings have revealed a robust correlation between certain oxidative stress parameters evaluated during the 12–20 weeks of gestation and PE (Ahmad et al., 2019). Increased levels of CAT were significantly linked to a diminished risk of PE. CAT is the only antioxidant found to be correlated with the severity of the illness, indicating a potential role for oxidative stress in the development of preeclampsia. The findings highlight the significance of oxidative stress markers in preeclampsia prediction and suggest that the pathophysiology of the disorder may entail imbalances between

oxidants and antioxidants. Placental markers have a great predictive power; in particular, pCAT's 100% sensitivity and specificity suggest that these markers could be used as preeclampsia diagnostic tools. This work sheds important light on the relationship between preeclampsia and markers of placental oxidative stress, demonstrating significant differences and robust predictive capabilities for specific markers. These results are important for understanding preeclampsia's underlying mechanisms and could assist in developing diagnostic strategies. Research has shown that creatinine levels measured in the first 20 weeks of pregnancy have a strong correlation with the onset of both mild and severe preeclampsia later in pregnancy (Tesfa et al., 2022). An increased risk of preeclampsia is linked to higher levels of creatinine early in pregnancy (Ambad & Dhok, 2019). The complex interplay between antioxidant defences and oxidative stress in preeclampsia is highlighted in this study, and the high diagnostic accuracy of placental catalase activity (pCAT) underscores the significance of these indicators in elucidating the pathophysiology of the condition.

These findings advance our comprehension of the molecular mechanisms underlying this complex pregnancy-related condition.

5.5 THE PREDICTIVE ACCURACIES OF PLACENTAL AND SERUM BIOCHEMISTRY MARKERS FOR PREECLAMPSIA

The fifth objective of the study was to evaluate and compare the efficacy of serum and placental biochemical markers in predicting preeclampsia. Systemic changes during preeclampsia are indicated by elevated serum levels of LDL, urea, AST, ALT, creatinine, BUN, and uric acid. Conversely, patients with preeclampsia exhibited lower serum levels of high-density lipoprotein cholesterol and a reduced estimated glomerular filtration rate. Among the eleven serum and eleven placental variables, creatinine was a

significant predictor of preeclampsia, with serum ALT and placental creatinine being the most predictive parameters. Elevated levels of total cholesterol, LDL, AST, ALT, urea, creatinine, BUN, and uric acid in serum during preeclampsia indicate systemic changes. However, there are more serum markers than placental markers for predicting preeclampsia. Elevated serum uric acid levels are associated with early-stage preeclampsia (Yue et al., 2023). Preeclampsia is linked to high blood uric acid levels before week 20 of pregnancy (Niraula et al., 2017; Yue et al., 2023), particularly within the first 8-12 weeks. This effect decreases with the duration of pregnancy, suggesting that high uric acid levels in the early stages of pregnancy, especially in the first 8–12 weeks, may be linked to the development of preeclampsia. As the weeks of pregnancy go by, this effect becomes less pronounced, indicating that high uric acid levels in the early stages of pregnancy may contribute to the development of preeclampsia.

Uric acid scavenges free radicals, particularly reactive oxygen species (ROS), which are known to inflict oxidative damage on cells (Becker et al., 1991). Uric acid helps lessen oxidative stress and its possible damage to cellular structures by scavenging these free radicals. Higher serum levels of uric acid, creatinine, BUN, urea, AST, ALT, total cholesterol, and LDL during preeclampsia indicate systemic alterations. These results highlight the fact that preeclampsia can present as systemic symptoms involving several organs, rather than only placental failure. Elevated levels of serum uric acid have been reported, especially in those with early-onset preeclampsia (Yue et al., 2023), suggests its potential role as a predictive marker for identifying this specific subgroup of patients. These alterations indicate potential cardiovascular and renal involvement, contributing to the overall clinical picture of the condition. Strong indicators of the pathophysiology of preeclampsia include placental catalase activity and creatinine,

which highlight the critical roles played by oxidative stress and renal function. (Alghifari et al., 2023; Sarween, 2020).

Remarkably, serum ALT exhibited exceptional predictive accuracy, suggesting its potential as a serum biomarker for preeclampsia. This discovery presents a fresh marker that may help with the disorder's early detection and observation. The lack of statistically significant link between serum and placental variables suggests that these markers may represent different features of the illness, highlighting the necessity of a thorough understanding and diagnosis of preeclampsia.

Placental and serum biomarkers contribute complementary information, suggesting a comprehensive approach to preeclampsia diagnosis. Serum ALT, a liver enzyme, stands out as a robust predictor, possibly indicating hepatic involvement in preeclampsia.

The elevation in values of hepatic enzymes among the preeclamptic pregnancies is a sure revelation of hepatic injury among this study group as compared with their counterparts in the control groups. Several studies have highlighted metabolic disturbances in preeclampsia, including abnormal lipid levels and elevated hepatic enzyme levels, suggesting that the disease has affected the liver (Asgharnia et al., 2017; GERA et al., 2023; Mou et al., 2021). Serum ALT is a useful diagnostic for preeclampsia because of its excellent predictive accuracy. Preeclampsia is associated with elevated blood levels of total cholesterol and low-density lipoprotein cholesterol (LDL); these levels indicate systemic disturbances in lipid metabolism, which may exacerbate the vascular and endothelial problems associated with PE women (Antonić et al., 2023; Singh et al., 2013). Increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels during preeclampsia suggest hepatic involvement, indicating that liver dysfunction could be part of the broader impact of the disease beyond cardiovascular issues. Moreover, elevated blood urea nitrogen (BUN),

creatinine, and urea levels indicate compromised renal function, which is frequently seen in preeclampsia. Preeclampsia has also been linked to elevated blood uric acid levels, which could be signs of oxidative stress and endothelial dysfunction, two factors crucial to the pathogenesis of preeclampsia (Bainbridge & Roberts, 2008; Corominas et al., 2022b). Uric acid has been linked to endothelial dysfunction and oxidative stress (Bo et al., 2008; Glantzounis et al., 2005; Kanellis & Kang, 2005),. Increased placental creatinine and uric acid levels highlight their possible roles in the pathophysiology of preeclampsia. These results imply that the systemic changes linked to preeclampsia may be caused by placental malfunction. Both are essential elements of the pathophysiology of preeclampsia

Placental catalase activity and creatinine emerge as strong predictors, emphasizing the role of oxidative stress and renal function in preeclampsia (Oztas et al., 2016). As a key organ throughout pregnancy, the placenta is essential to the control of several functions. One liver enzyme that is emphasised as a remarkable indicator of possible hepatic involvement in preeclampsia is serum ALT. The overall complexity of preeclampsia may be attributed to abnormal liver function, and ALT is a strong serum indicator of this condition. This highlights the necessity for a comprehensive knowledge of preeclampsia that takes into account the involvement of several organ systems.

The results of this study highlight the complexity of preeclampsia, a condition linked to notable changes in a number of biochemistry indicators. The placenta's elevated levels of uric acid and creatinine point to a possible role for these substances in the pathogenesis of preeclampsia. These indicators might point to reduced renal function and oxidative stress in the placental tissue, which would hasten the disease's onset. The current study emphasises the significance of various markers by shedding light on the changes in placental and serum biochemistry variables in preeclampsia. The

comparative analysis of predicted accuracies highlights the potential clinical relevance of particular variables and highlights the need for a comprehensive approach to the diagnosis and understanding of preeclampsia.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

6.1 SUMMARY OF FINDINGS:

The study aimed to investigate how preeclampsia correlates with various maternal characteristics, revealing notable associations with Caesarean sections, preterm deliveries, abnormal outcomes, and placental malaria. It found that maternal obesity, indicated by a higher BMI, was associated with a higher incidence of preeclampsia in comparison to pregnancies with normotension.

This emphasises how crucial it is to control a mother's weight and overall health throughout pregnancy in order to lower her risk of developing preeclampsia. Promising results were observed for the Neutrophil-to-Lymphocyte Ratio (NLR) and the Monocyte-to-Lymphocyte Ratio (MLR) in the investigation of potential prognostic indicators for preeclampsia. On the other hand, MLR showed better diagnostic accuracy than NLR, with identical specificity and higher sensitivity, indicating that it may be a more accurate predictor of preeclampsia.

Variations in blood pressure were found to affect placental oxidative stress markers, with systolic blood pressure having a greater impact than diastolic blood pressure, especially on Total Antioxidant Capacity (TAC). This underscores the complex interplay between blood pressure, oxidative stress, and placental health during pregnancy.

Notably different placental oxidative stress indicators, including Oxidative Stress Index (OSI), Total Catalase (CAT), Antioxidant Capacity (TAC), and Malondialdehyde (MDA), were observed in preeclampsia. Among these, placental

creatinine, MDA, TAC, CAT, and Total Peroxide (TP) demonstrated considerable predictive potential, with CAT emerging as a highly accurate predictor.

Systemic changes in preeclampsia were reflected in serum biochemistry markers, including elevated total cholesterol, LDL, AST, ALT, urea, creatinine, BUN, and uric acid. Serum ALT showed exceptional predictive accuracy, suggesting potential liver involvement. The lack of a significant correlation between placental and serum variables highlighted their distinct roles in representing different facets of the disease.

6.2 LIMITATION OF THE STUDY:

Despite significant findings, this study had certain limitations:

1. **Population Specificity**: The study's findings are based on a specific population, and extrapolation to broader demographics requires validation.
2. **Retrospective Data Limitations**: The retrospective nature of some data may introduce biases and limitations in capturing real-time associations.
3. **Potential Confounding Variables**: The study may not encompass all potential confounding variables, necessitating further comprehensive investigations.
4. **Dynamic Interactions Exploration**: Further studies are necessary to examine how different markers interact with each other and their collective predictive capabilities.
5. **Need for External Validation**: External validation and replication of the study in diverse cohorts are essential to enhance the generalizability of the findings.

6.3 CONCLUSION:

Preeclampsia is associated with a number of harmful effects, including Caesarean deliveries, preterm births, and placental malaria. Increased maternal obesity, as indicated by a higher BMI, is a contributing factor, highlighting the importance of proactive maternal health management.

When it comes to predicting preeclampsia, the Monocyte-to-Lymphocyte Ratio (MLR) performs better diagnostically than the Neutrophil-to-Lymphocyte Ratio (NLR). Because they demonstrate how elements of the immune system contribute to the disease's development, both ratios are valuable as predictive markers.

Blood pressure fluctuations affect placental oxidative stress markers, with systolic blood pressure having a more significant impact. This research improves the understanding of how blood pressure, oxidative stress, and placental health interrelate during pregnancy.

Placental oxidative stress markers, particularly Catalase (CAT), display notable differences in preeclampsia and exhibit strong predictive potential. These results support the investigation of new biomarkers for early detection and management of preeclampsia.

Serum Alanine Aminotransferase (ALT) stands out as a highly accurate predictor, indicating possible liver involvement in preeclampsia. The lack of a substantial link between serum and placental variables highlights the necessity of a thorough diagnostic process.

6.4 RECOMMENDATION:

We recommend that policymakers and stakeholders consider;

1. Implementing proactive measures for maternal health, including weight management, to mitigate the risk of preeclampsia associated with higher BMI.
2. Further investigate and validate the potential of MLR and other immune system components as predictive markers for preeclampsia in larger and diverse populations.
3. Both systolic and diastolic blood pressure are important for monitoring and managing preeclampsia, as they have varying effects on placental oxidative stress markers.
4. Exploring the clinical utility of placental oxidative stress markers, particularly CAT, as potential diagnostic tools for preeclampsia.
5. Evaluation of the significance of serum ALT as a serum biomarker for preeclampsia and investigation of its role in hepatic involvement in the condition.

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APPENDIX

6.6 APPENDIX 1: SUBSTRUCTURED QUESTIONNAIRE

RESEARCH QUESTIONNAIRE VERSION 1.0

STUDY TITLE:
SECTION A: PERSONAL /DEMOGRAPHIC DATA
ID NO: ……. DELIVERY DATE:.. …/……/…….
1. AGE:……(yrs).
2. BLOOD GROUP: [ ] A [ ] B [ ] AB [ ] O: Rhesus factor:[ ] Pos. [ ]Neg.
3. SICKLING STATUS: [ ] Positive [ ] Negative
4. GESTATIONAL AGE: (Weeks)
5. OCCUPATION: …….....
6. AREA / RESIDENT:.....
SECTION B: OBSTETRIC AND CLINICAL DATA
7. PARITY: ……..... GRAVIDITY:.....
8. EXPECTED DATE OF DELIVERY:…….
9. WEIGHT: .....(Kgs) HEIGHT: (M)
10. BODY MASS INDEX: [Weight kg/ (Height (m)2]).
11. BLOOD PRESSURE: (mmHg)
12. NUMBER OF BABIES DELIVERED: One [ ] Two Yes [ ] three [ ] others [ ]
13. MODE OF DELIVERY: self-delivery [ ] assisted delivery [ ] caesarian delivery [ ]
14. DELIVERY COMPLICATION; placenta abruption [ ] preterm [ ] premature rupture of membrane [ ] Placental Acrecia [ ] Placental Previa [ ] Premature labour [ ]Placental Obstructions [ ]
15. MATERNAL OUTCOME; Severe eclampsia [ ] Pre-eclampsia [ ] Gestational hypertension [ ] Gestational diabetes [ ] Maternal Demise [ ]
16. FOETAL OUTCOME; stillbirth [ ] Trisomy-21 [ ] Trisomy-18 [ ] Blighted ova [ ] Spina Bifida [ ] Anencephaly [ ] Polyhydramnios [ ] Hydrocephalus [ ] Intrauterine growth retardation [ ] Others…….
17. BABY'S WEIGHT :……...gm
18. MOTHER'S WEIGHT :……..Kg
19. 1 MINUTE APGAR SCORED:…… 5 MINUTE APGAR SCORED…..

SECTION C: PLACENTA DATA
20. PLACENTA DIMENSIONS; Length..….cm, Width……cm, Thickness……..cm, Weight…….gm
21. PLACENTA SHAPE; Round [ ] Oval [ ] Irregular [ ] Succenturiate lobes [ ]
PLACENTA MEMBRANE CHARACTERISTICS;
22. INSERTION; Marginal [ ] circummarginate [ ] circumvallate [ ]

23. COLOUR; Clear [ ] Semi opaque [ ] Opaque [ ]
24. OTHER ABNORMALITY ON MATERNAL SURFACE (PLACENTA); complete [ ] Incomplete [ ] Ragged [ ]
25. OTHER ABNORMALITY ON FOETAL SURFACE (PLACENTA); …….
26. FOCAL LESIONS ON CUT SURFACE; Yes [ ] No [ ] Size;……% POSITION; marginal [ ] Eccentric[ ] Central [ ] Multiple [ ]
27. MACROSCOPICALLY IDENTIFIABLE DIFFUSE LESIONS; Yes [ ] No [ ] %.....,,,,,,,,,,
28. UMBILICAL CORD INSERTION; Central [ ] Paracentral [ ] Eccentric [ ] Marginal [ ] Velamentous [ ]
UMBILICAL CORD:
29. LENGTH:…….cm,
30. AVERAGE DIAMETER……...cm
31. NUMBER OF VESSELS;……
32. UMBILICAL CORD TWISTS; under coiled [ ] Normal [ ] Hyper twisted [ ]
33. UMBILICAL CORD TRUE KNOTS; Yes [ ] No [ ]
34. Do you have any additional information?.....
……
……
Signature/Thumbprint of subject: ……
…….
Name/Signature of Clinician: ……
Name/ Signature of Interviewer: ……