IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 11 Ser. 3 (November. 2024), PP 39-105
www.iosrjournals.org

Neutrophil-Lymphocyte Ratio, Platelet- Lymphocyte Ratio And Mean Platelet Volume In Second Trimester Pregnancy For Prediction Of Preeclampsia

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Date of Submission: 28-10-2024 Date of Acceptance: 08-11-2024

INTRODUCTION

Preeclampsia (PE) is a condition that occurs exclusively during pregnancy with multisystem involvement due to widespread endothelial dysfunction and vasospasm and affects 2-10% of pregnancies worldwide and 8-10% of pregnancies in Indian women [1,2]. The incidence of PE is 7 times higher in developing countries compared to developed countries (WHO 2005) [3–5]. PE is defined by new onset hypertension in a previously normotensive woman, presenting after 20 weeks of pregnancy with a systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg on 2 occasions at least 4 hours apart, with or without proteinuria ≥300mg/24hrs or a protein/creatinine ratio ≥0.3 or a urine dipstick reading of 2+, or in the absence of proteinuria, new onset hypertension accompanied by any one of the following recent onset of any of the following: thrombocytopenia (platelet < 100 $x10^9$/L), renal insufficiency (serum creatinine >1.1mg/dL), impaired liver function (liver transaminases more than twice the normal), pulmonary edema, new onset headache unresponsive to medication or visual symptoms [6].

PE is a leading cause contributing to 10-15% of maternal deaths and 20-22% of perinatal deaths, especially in lower and middle-income countries, due to eclampsia, placental abruption, HELLP syndrome, congestive heart failure and intracranial hemorrhage, renal failure, pulmonary edema, uteroplacental insufficiency, FGR, and prematurity [7–11]. In addition to immediate feto-maternal adverse outcomes, evidence suggests the future risk of hypertension, cardiovascular diseases, and stroke in PE women and their offspring [12–14].

In developing countries like India, the healthcare system is continuously challenged by the substantial burden of infectious diseases, anemia, non-communicable diseases like diabetes, hypertension, cardiovascular diseases, etc., and recently the COVID-19 pandemic. Complicated pregnancies further add to a substantial burden to the already hard-pressed healthcare delivery system. Hence early prediction of complicated pregnancies with timely referral of only those at high risk of complications can reduce the burden on the healthcare delivery system.

Early prediction and effective management of PE, especially in lower and middle-income countries, is crucial to achieving the sustainable development goal targets of the WHO of reducing MMR to < 70/1,00,000 live births and PNM to <50 per 100 live births by 2030 globally and mitigating the future risk and burden of non-communicable diseases in both mothers and their offspring and future generations from PE [9,12–14].

The etiopathogenesis of preeclampsia (PE)

Disordered remodeling of uterine spiral vessels in the uterus: The main etiopathogenesis of PE has been attributed to disordered remodeling of maternal spiral arteries due to disordered invasion of trophoblasts into maternal spiral vessels. This results in inadequate placentation, reduced placental perfusion, hypoxia, and vasospasm, causing oxidative stress. The resultant oxidative stress leads to buildup of peroxides and superoxide anions and a reduced synthesis of nitric oxide. Preeclampsia has been proposed to be caused by extensive inflammation, damage to the vascular endothelium, and platelet aggregation [15–18].

Dysregulated immune response: In normal pregnancy, a shift in immune response from proinflammatory Th1 to an anti-inflammatory Th2 response is crucial for the sustenance and survival of the fetal allograft. [16,17]. In normal pregnancy, studies have reported increased expression of Th2 cytokines IL-4 and IL-10 over Th1 cytokines and IL-2 at not only the peri-implantation endometrium at the feto-maternal interface but also in stimulated peripheral blood mononuclear cells (PBMC) [19,20]. Emerging data suggests a dysregulated immune response in Preeclamptic women with Th1 predominance (↑ IL6, IL8, IL2, & TNF alpha) and a reduced Th2 response (↓IL10). Isolates of PMBC in women with preeclampsia have also been reported to have a predominance of Th1 cytokine responses [19,20].

Role of Neutrophils/NLR in PE: The Proinflammatory Immunological Response with ↑ Neutrophil count, neutrophil activation, exaggerated function, and neutrophil extracellular traps (NETs) are reported to play an important role in the pathogenesis of PE by causing oxidative stress and endothelial cell dysfunction [21–23] which causes thrombocyte activation, vasoconstriction, hypertension, and end-organ ischemia [24]. Some authors have reported a higher leukocyte count with increased neutrophils and reduced lymphocytes and a higher neutrophil-to-lymphocyte ratio (NLR) in PE women compared to women with a normal pregnancy [24–34]. While others have reported no appreciable variations in NLR in women with PE as compared to normal pregnancies [11,25,35]. Contrary to these, a few others have suggested reduced NLR in PE women [36,37]. Some studies have suggested that NLR can predict PE and its severity [30,31,38], while others have reported no such association [28]. Therefore, the studies on the role of NLR in PE are not only inconsistent but also inconclusive.

Role of Thrombocytes in pathogenesis of PE

Platelet count/PLR: Platelet activation in response to ischemia and endothelial dysfunction is reported as an important player in the pathogenesis of PE through cytokine-mediated immune response [18]. Some studies have reported low platelets in PE women in response to platelet activation along with increased consumption [11,25,28,36,39–45]. Contrary to this, others have reported a significant increase in the platelet count in PE women as compared to women with normal blood pressure [46]. Platelets and lymphocytes both play a crucial role in cytokine dependent immune responses and immune surveillance. Some studies have reported a significant increase in PLR in PE women as compared to normotensive women [11,29,46,47]. Contrary to this, others have reported a significantly reduced PLR in PE women [23,42,48–50]. While others have found no association of PLR and with PE[51–55]. Hence, the role of PLR in PE remains inconclusive due to the inconsistencies amongst studies.

MPV (mean platelet volume): Platelet volume, an indicator of platelet size, reflects platelet reactivity. Larger platelets show increased aggregation and expression of thromboxane and adhesion molecules [56,57]. Various authors have reported increased MPV in preeclamptic women associated with increased turnover of platelets [25,28,36,40–43,45,46,52,58,59], while others have found no association of MPV with PE [11,42,51][60,61]. Hence, there are inconsistencies on MPV and PE in existing data.

Early prediction of preeclampsia (PE) can be enhanced using the uterine artery pulsatility index (PI) and various biomarkers that indicate endothelial damage and vascular growth. Notably, VEGF, PLGF, PAPP-A, and sFlt-1 have emerged as promising tools with significant potential for the early detection of PE [62–64]. However, due to the high cost and limited availability in low resource setups, these tools are not easily accessible to majority of population. Therefore, there is an urgent need to explore the cost effective easily available methods for early prediction of PE in low resource settings. Given the role of inflammatory markers in the pathogenesis of PE and the inconsistencies in existing literature, we focused on studying the following inflammatory markers: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) in the second trimester of pregnancy (16-24 weeks) for early prediction of preeclampsia, as these markers are easily measurable, inexpensive, widely available, and part of routine antenatal lab investigations.

REVIEW OF LITERATURE

Gezer et al. (2016)[29] in their retrospective study tried to determine whether 1st trimester NLR and PLR could be used in early prediction of subsequent preeclampsia this study was conducted on 209 women between 22-40 weeks of gestation who had developed preeclampsia they took 220 normotensive pregnant women as controls they retrospectively analysed and compared the inflammatory markers leukocyte, neutrophil, lymphocyte, platelet, NLR and PLR values of 1st trimester in these two groups of women. They noted that at a NLR cut-off 3.08, and PLR at a cut off 126.8 had a sensitivity of 74.6% and 71.8% and specificity of 74.6% and 72.4% respectively for prediction of preeclampsia. On ROC curve analysis they also noted that AUC 0.716, $p<0.001$ and PLR had an AUC 0.705, $p<0.001$ showing them to be very good predictors for preeclampsia. They suggested that NLR and PLR being inexpensive, rapid and easily available could be used for early prediction of preeclampsia and those with high NLR and PLR should be closely monitored for the sign's preeclampsia i.e. hypertension and protein urea.

Gogoi et al. (2019)[11] in their cross-sectional study done on 134 women of which 67 women diagnosed with preeclampsia diagnosed at term and 67 were in the control normotensive group in whom the inflammatory markers were done and compared. They reported a significantly higher NLR, PLR and MPV with $p<0.05$. Though the platelet count was notably lower in women with pre-eclampsia, while the differences in PDW and Pct between pre-eclamptic pregnant women and the control group were lower but not statistically significant. They came to the conclusion that prenatal follow-up NLR and PLR can be utilized to predict the risk of preeclampsia.

Mannaerts et al. (2019)[42] in a retrospective study done on 118 preeclamptic subjects and 1495 normotensive control subjects. These subjects were divided into 2 groups the Preeclamptic and normotensive control group and the hemogram report of these subjects before 20 weeks of pregnancy and in later half of pregnancy after development of preeclampsia were retrieved from the hospital records and compared. The authors reported no significant difference in NLR and PLR estimated before 20 weeks of pregnancy, between the PE and control group. However, they noted significantly higher MPV in PE group (8.64±1.17 fL) as compared to control group (8.06±0.87 fL), $p = 0.006$. However, the same authors noted a significantly higher NLR, higher MPV, but a low PLR in PE group compared to the control group in late pregnancy after 20 weeks ($p<0.05$). These suggested that before 20th week of

pregnancy, only MPV was predictive for future development of preeclampsia unlike NLR and PLR.

Panwar et al. (2019)[31]Conducted a prospective case control study on 440 low risk primigravida's between 16-18 weeks of gestation of these 64 women i.e. 14 % developed preeclampsia of which 25 (39%) developed severe preeclampsia and 376 women remain normotensive. They estimated the NLR on blood samples drawn from these enrolled women in the second trimester of pregnancy. They reported a significantly higher NLR of 5.55±0.81 among preeclamptic women compared to normotensive women NLR 4.5±0.66, p<0.001. They also reported significantly higher NLR in severe preeclamptic women 6.08±0.43 compared to 5.39±0.84 among women with mild preeclampsia p=0.001they also noted that at NLR cut off 5.6 had a high sensitivity of 73.4% and 88.6% specificity with AUC 0.84 in the prediction of prediction. They concluded NLR was useful marker for only prediction of preeclampsia also its severity.

Singhal et al. (2019)[63] in their case control study done on 70 pregnant women of which 35 were preeclamptic and 35 were normotensive control subjects this study was done after 20 weeks of gestation when venous sample were drawn from all the enrolled women for NLR. They found a significantly higher NLR (5.64 ±1.78) in the preeclamptic group vis-à-vis (4.19 ± 1.00) in normotensive control group, p<0.001. They also reported, that NLR cut-off of ≥4.86 could predict preeclampsia with a sensitivity 68.6% and a specificity of 80% and PPV of 77.4% and NPV of 71.8% and accuracy of 74.3% with an AUC of 0.739, p=0.001. They suggested that periodical NLR in high risk women to be done during the ANC follow up for early prediction of preeclampsia.

Zheng et al. (2019)[66] They did a systematic review and meta-analysis of 7 studies to assess the diagnostic value of NLR in preeclampsia. They reported a pooled sensitivity of 0.74 (95% CI 0.71–0.76) and specificity of 0.64 (95% CI 0.61–0.68), a positive likelihood ratio of 2.62 (95% CI 1.79–3.84) and a negative likelihood ratio of 0.34 (95% CI 0.24– 0.48), the Diagnostic odds ratio of 8.44 (95% CI 4–17.78), and AUC of 0.82, for Neutrophil Lymphocyte Ratio (NLR) in prediction of PE. They reported that NLR as biomarker has a moderate diagnostic and predictive value for Preeclampsia. They concluded that NLR had an acceptable sensitivity as diagnostic marker for preeclampsia but not better specificity and they suggested future studies with larger sample to verify the role of NLR alone or with combination with other marker for prediction of preeclampsia.

Wang et al. (2019)[47] In their case control study done in the 3rd trimester of pregnancy compared NLR and MLR (Monocyte-lymphocyte ratio) in preeclamptic versus normotensive women. Among 463 recruited subjects 302 women with preeclampsia and 161 pregnant normotensive control group. They reported a significantly higher NLR in PE group 4.60±1.83 vis-à-vis 3.51±0.82 in the control group p=0.01. NLR at a cutoff 4.18 had a sensitivity of 69.68% and specificity of 63.95% and AUC 0.71 PPV 67%, NPV of 66.67% with a likelihood ratio of a test of 1.93. They concluded that WBC which is gold standard for monitoring inflammatory diseases has a great potential in prediction of preeclampsia due to its convenience simplicity and good sensitivity.

Sweed et al. (2021)[23] In their prospective study conducted on 70 women, sampled the subjects twice, once just before labour and in the first 48 hours of delivery. They also noted the N/L ratio from the early pregnancy records done before 20th week of pregnancy. The subjects were divided into two groups of 35 each, with and without preeclampsia.

They reported no statistically significant difference in N/L ratio between preeclamptic vis-a-vis normotensive control group with N/L ratio value of 4.01±1.3 and 3.66±0.35 respectively, p=0.14. On the contrary the same authors reported a statistically significant difference in the N/L ratio in the sample drawn in the first 48 hours of delivery between the preeclamptic and normotensive with the mean N/L ratio 4.22 ±1.51 and 3.66 ± 0.35 respectively, P=0.04, However they reported that the N/L ratio was not able to discriminate between preeclamptic and normotensive controls with an AUC of 0.56, standard error 0.07, CI 95%, 0.41-0.71.However they found that NLR prior to 20 weeks of pregnancy had no predictive ability for PE, with p =0.17.

Oglak et al. (2021)[48] In a retrospective case control study compared the NLR, PLR and MPV on 301 subjects from 24-40 weeks of pregnancy which included 94 mild PE, 107 severe PE and 100 normotensives controls. They retrieved the CBC counts of all included subjects between 6-14 weeks of pregnancy from the records. They discovered that first trimester NLR was considerably higher in the preeclamptic group compared to the normotensive group, but it was not a significant predictor of the preeclampsia's severity. With value of NLR in mild PE 4.3±1.4 and in serve PE 4.6±1.8 and in the normotensive 3.1±1.1 and p value <0.001. PLR was also found to be significantly higher in preeclamptic vis-à-vis normotensive group but cannot differentiate between mild and severe cases with value of PLR in mild PE 137.1±44.9 and in severe PE 138.1±38.2 and in the normotensive group 121.1±27.4 with control versus mild PE

p-value=0.016 and control versus severe PE p-value=0.020 and mild PE versus severe PE p value=0.988. They also noted a significantly higher MPV in PE and in severe PE group as compared to normotensive group with value in mild PE 10.6±2.3 fL and in severe PE 11.2±1.4 fL and in normotensive group 10.3±1.3 with p-value<0.001. On ROC curve analysis they reported that NLR cut off 4.1 could predict PE with a sensitivity of 82% and specificity of 62%, MPV cut of 10.65 fl could predict PE with sensitivity 63.7% and specificity 65% respectively. They also suggested that PLR cut of 131.8 could predict PE with sensitivity 65% and specificity of 60.2%. They reported that first trimester NLR, PLR and MPV values were significantly higher in patients who developed PE later on. However, these markers cannot discriminate between mild and severe PE.

Singgih et al. (2021)[08] in a cross-sectional observational study conducted on 924 pregnant women in their 3rd trimester of which 838 women were normotensive and 86 pregnant women with preeclampsia they evaluate the effectiveness of the Neutrophil–Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), and Mean Platelet Volume (MPV) in predicting preeclampsia in pregnant women. The findings showed a significant increased NLR and MPV values between the two groups preeclamptic vis-à-vis normotensive group with mean NLR in PE group 7.55±5.44 and in normotensive group 6.07±4.93, p-value=0.004 and mean MPV in PE group 8.72±0.98 fL and in normotensive group 8.38±0.92 fL, p-value=0.002. However, PLR was not found to be statistically significant p-value=0.878. On ROC curve analysis NLR yielding an AUC of 0.595 (p=0.035), reflecting a low predictive capability. The study concluded that while NLR can help distinguish between preeclampsia and normotensive cases, its predictive ability is limited.

Sachan et al. (2022)[09] in a prospective case control study done on 100 subjects between 13-20 weeks of gestation studied the diagnostic accuracy of N/L ratio for severe and non-severe preeclampsia .100 subjects were equally divided into 50 PE and 50 healthy controls, out of which 34 were mild PE and 16 severe PE. The participants were sampled twice, first at enrolment and second after development of preeclampsia and N/L ratio was estimated from samples. On analysis of N/L ratio done before 20th week, they reported a significant higher difference in N/L ratio in the mild PE (3.38±0.16) and severe PE (4.26±0.31) vis-a-vis non-PE control group (p<0.01) and also significantly higher N/L ratio between the mild vis-a-vis severe PE (p<0.001) suggesting the discriminatory ability of NL ratio for prediction of severity of PE. The authors also reported that N/L cut-off of >3.35, had a promising diagnostic accuracy for

prediction of PE using ROC curve analysis AUC =0.75, p=0.01, sensitivity 52.9% and specificity 74.5%. They suggested that maternal N/L ratio should be considered not only for prediction of PE but also for evaluation of severity of PE.

Daud et al. (2022) [70] In a retrospective cross-sectional study to determine the predictive values of Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), and Mean Platelet Volume (MPV) for pre-eclampsia. This study included 161 pregnant women, of whom 79 were pre-eclamptic and 82 were normotensive subjects. They found that MPV was significantly higher in the pre-eclamptic group (7.10 fL) compared to the normotensive group (6.90 fL), with a p-value of 0.02. ROC curve analysis showed MPV at an optimal cut-off of 10.4 fL, with an AUC of 0.609 (95% CI 0.522-0.696; p=0.02), had a sensitivity of 44.8% and a specificity of 40%. There was no significant association between NLR and PLR and pre-eclampsia (p > 0.05). The study concluded that MPV is a better predictive marker for pre-eclampsia in pregnancy.

Purandare et al. (2022) [54] in a retrospective case control study conducted on 67 preeclamptic subjects and 70 normotensive subjects in the 3rd trimester of pregnancy to find the role of NLR, and PLR in the diagnosis of preeclampsia. They found that NLR was significantly lower in pre-eclampsia with mild features (4.03±2.05) compared to the normotensive group (5±2.68) with a p-value of 0.034. However, no statistically significant difference was observed when comparing the normotensive group with severe pre-eclampsia (p=0.172). Although the mean PLR was lowest in the severe pre-eclamptic group compared to the normotensive and mild pre-eclampsia groups (97.49±61.56, 109.02±51.88, and 118.92±58.62, respectively), the differences were not statistically significant (p>0.05). Despite the significance of the NLR value in mild pre-eclampsia cases, the study concluded that the association of NLR and PLR with pre-eclampsia remains inconsistent, highlighting the need for larger prospective studies with trimester-wise follow-up.

Corduneanu et al. (2023)[50] in a prospective cohort study done on 107 pregnant women. Out of total subjects enrolled 88 had gestational hypertension (GH) and 19 had preeclampsia (PE). The study aimed to find the role of NLR and PLR levels for prediction of preeclampsia. They noted that PLR was significantly lower in the PE group (85.47±7.91) as compared to the GH group (115.90±4.63) p=0.005. However, there was no statistical difference of NLR between the two groups 3.51±0.12 in the PE group and 3.76±0.26 in the GH group p=0.40. They suggested that PLR <85.47 cutoff can be used as a diagnostic marker in preeclampsia but a larger study is needed to prove an association of these markers and preeclampsia.

Sabry et al. (2024)[71] In cross-sectional study of 128 pregnant women divided into two equal groups (64 with pre-eclampsia and 64 without), the role and association of Neutrophil to Lymphocyte Ratio (NLR) and Platelet indices with pre-eclampsia were explored. The study found a significant increase in NLR and PLR in the pre-eclamptic group compared to the normotensive group, with mean NLR values of 4.3±1.06 in the pre-eclampsia group and 2.9±0.68 in the normotensive group (p-value <0.001), and mean PLR values of 141.2±34.8 in the pre-eclampsia group and 113.4±28.1 in the normotensive group (p-value <0.001). Multivariate regression analysis revealed that each unit increase in NLR (OR 1.49, 95% CI 1.33-1.81; p-value = 0.004) and PLR (OR 1.51, 95% CI 1.15-1.72; p-value = 0.006) increased the risk of having pre-eclampsia. The study concluded that NLR and PLR are significantly higher in the pre-eclamptic group than the normotensive group and can be utilized to distinguish between the two groups.

LACUNAE IN THE LITERATURE

There are studies of association of preeclampsia and its severity using various expensive biomarkers like PAPPA-A, PLGF, Sflts. However, the studies on the association of the mean platelet volume in the second trimester of pregnancy, the neutrophil-lymphocyte ratio, and the platelet-lymphocyte ratio with PE and its prediction are inconsistent and conflicting. There is paucity of data on the combined use of NLR, PLR and MPV in prediction of PE.

RESEARCH QUESTION

Does combined values of NLR, PLR and MPV in the second trimester increases the predictive value of preeclampsia?

AIMS AND OBJECTIVES

AIM

To observe the role of NLR, PLR and MPV in the prediction of the development of preeclampsia.

OBJECTIVES

Primary Objective-

To find the utility of systemic inflammatory markers like NLR, PLR and MPV in second trimester of pregnancy for prediction of preeclampsia.

Secondary Objectives

To find association of maternal NLR, PLR and MPV in second trimester with-

1. Severity of Pre-eclampsia
2. Adverse neonatal outcome
    - Preterm deliveries
    - Low birth weight (<2.5kg)
    - Meconium stained liquor
    - Low APGAR (<7 at 5 min)
    - NICU admission
    - Neonatal death

MATERIAL AND METHODS

Study Area: The study was conducted after approval of institutional ethics committee and written informed consent. The participants were selected from the Antenatal clinic of Department of Obstetrics and Gynaecology ESIC Model Hospital Noida sector-24, Uttar Pradesh.

Study Population: Patients who came to ESIC Model Hospital Noida Uttar Pradesh for antenatal visits and delivery.

Study Design: This study was a prospective, observational study.

- **Sample Size**: Oglak et al. (2021) found significantly higher white blood cell counts, NLR, and PLR in preeclamptic patients ($p < 0.001$ and $p = 0.016$, respectively). NLR (cut-off 4.1), MPV (cut-off 10.65 fl), and PLR (cut-off 131.8) were identified as useful early markers for predicting preeclampsia with respective sensitivities and specificities of 82%/62%, 63.7%/65%, and 65%/60.2% and stated that preeclampsia complicates around 2-8 % of all pregnancies. The prevalence of PE in hospital practice varies from 5-15%, considering the prevalence of preeclampsia approximately 10%, the minimum required sample size with desired precision of 5%, 80% power of study and 5% level of significance, to reduce margin of error. And the sample size was calculated using the following

  Sample size(n) = $Z_{\alpha/2}^2 \times p \times (1-p) / MOE^2$

  MOE is the margin of error, p is the *sample* proportion, and N is the population size.

  Margin of error (MOE)=0.05(5%)

  Prevalence/sample proportion p=0.10 (10%)

  Confidence level =95% ($Z\alpha/2 \approx 1.96$)

  Sample size (n)= $(1.96)^2 \times (0.10) \times (1-0.10) / (0.05)^2$

  Calculated sample size (n) =138.29

  Considering the dropouts of 10 % from the study the total sample size included in our study was 150.

Formula used is for testing sensitivity and specificity of single diagnostic test:

1) For sensitivity.

$$n = \left(Z_\alpha \times \sqrt{Se \times (1 - Se)} + Z_\beta \times \sqrt{Se_1 * (1 - Se_1)}\right)^2 / difference^2$$

where Se is sensitivity

$Z_{\alpha/2}$ is value of Z at two sided alpha error of 5% and Z_β is value of Z at power of 80%

2) For specificity:

$$n = \left(Z_\alpha \times \sqrt{Sp \times (1 - Sp)} + Z_\beta \times \sqrt{Sp_1 * (1 - Sp_1)}\right)^2 / difference^2$$

where Sp is specificity

$Z_{\alpha/2}$ is value of Z at two sided alpha error of 5% and Z_β is value of Z at power of 80%.

Inclusion criteria:

1. Singleton pregnancy
2. Second trimester pregnancy (16-24 weeks)
3. Primigravida and multigravida (age 18-37 years).

Exclusion criteria:

1. Past h/o preeclampsia in previous pregnancy
2. Known case of hypertension
3. Medical disorders
    - Hypothyroidism
    - H/O GDM in previous pregnancy
    - Overt Diabetes
    - Kidney disease, pyelonephritis, nephrolithiasis
    - Liver disorders HBV, HEP-A, C, E, chronic liver disease
    - Gall bladder cholelithiasis
    - Collagen vascular diseases

- Epilepsy
- H/0 IBD/RA/SLE/Autoimmune diseases
- Cardiovascular disease
- Neurological disease, Epilepsy

4. Bad obstetrics history (recurrent pregnancy loss)
5. H/O Fever within 4 weeks, current systemic infection.
6. APLA Syndrome
7. Multiple pregnancy
8. Trophoblastic disease
9. H/O Alcohol or tobacco use in any form smoking, antidepressant drug and substance abuse.
10. BMI <18 and >35

Study Duration

This Prospective observational study was conducted over 2 years of duration (2022-2024).

MATERIAL

1. Sample vial (EDTA VIAL).
2. 5ml Syringes with needle.
3. CBC Machine
4. Digital BP machine

METHODS

This prospective observational study was conducted in the Department of obstetrics and gynaecology of ESIC Model Hospital Noida, after the approval of the institutional ethics committee. Total of 150 antenatal subjects with 16-24 weeks of period of gestation were enrolled for study after taking written informed consent and aforementioned inclusion and exclusion criteria were applied. After enrolment 3 ml venous blood samples was collected in EDTA vial and immediately sent to pathology lab for testing inflammatory markers. After

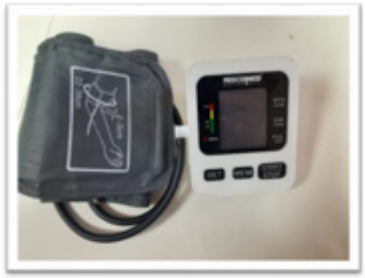
enrollment subjects were asked to attend the routine ANC fortnightly till 36 weeks and there after weekly till delivery or the expected date of delivery. At each antenatal visit, subjects were screened for weight, Blood Pressure (SBP & DBP) in sitting position in both arms using a Calibrated Aneroid Sphygmomanometer. The patients BP was recorded in sitting position, not cross legged, with arms resting on the table using an appropriate cuff size of the BP apparatus based on mid arm circumference. 2 BP readings were taken in each arm right and left, 5 minutes apart and a mean of the 4 readings taken, were noted. The participants were also be screened at each visit including screening for pedal edema, urine albumin, fetal growth and wellbeing. USG biometry was performed as per hospital protocol for low risk pregnant women. They were watched closely till delivery for onset of any adverse maternal and neonatal complications. At delivery, note was made of any neonatal adverse outcomes.

Maternal blood was analysed for.

- NLR
- PLR
- MPV

Sampling technique- Subjects enrolled in the study were sampled. Blood sample (3 ml) of the participants were collected under all aseptic precautions for CBC parameters in EDTA vial and tested on the same day within 2 hours of collection for Complete blood counts (CBC) including Neutrophil-lymphocyte ratio (NLR), Platelet-lymphocyte ratio (PLR) and Mean platelet volume. Analysis on 6 PART AUTOMATED HAEMATOLOGY ANALYSER RAPID DIAGNOSTIC PVT LTD. MINDRAY-BC-6200, TW-8B000279 was done to calculate absolute neutrophil count and lymphocyte counts using flow cytometry with fluorescent staining, and platelet counts using the DC impedance method. Note was made of N/L ratio and P/L ratio and MPV.

[6 PART AUTOMATED HAEMATOLOGY ANALYSER RAPID DIAGNOSTIC PVT. LTD. MINDRAY-BC-6200 TW-8B000279].



[DIGITAL B.P] APPRATUS].

[E.D.T.A VIAL].

[5 ml SYRINGE with needle].

STATISTICAL ANALYSIS

- Categorical variables were reported as numbers and percentages (%), while continuous variables were presented as mean ± standard deviation (SD) and median.
- Normality of data was tested by Kolmogorov Smirnov test. If the normality was rejected, then a non-parametric test was used.
- Quantitative variables were compared using Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups (with or without pre-eclampsia).
- The Fisher's exact test and the Chi-Square test were used to compare qualitative variables. The diagnostic test yielded results for sensitivity, specificity, NPV, and PPV calculations.
- Univariate logistic regression was used to find out odds ratio of Neutrophil-lymphocyte ratio (NLR), Platelet-lymphocyte ratio (PLR) and Mean platelet volume as predictor for pre-eclampsia.
- Univariate and multivariate linear regression were used to find association of above variables with PE.
- One regarded a p-value of less than 0.05 as significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

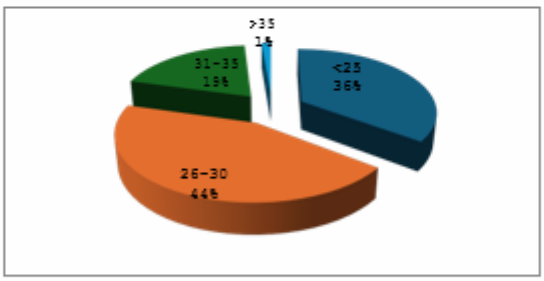
OBSERVATIONS AND RESULTS

- **PATIENT DEMOGRAPHICS**

TABLE 1: AGE WISE DISTRIBUTION OF SUBJECTS

AGE	No. of cases	Percentage
< 25	53	35.3%
26-30	66	44.0%
31-35	29	19.3%
> 35	2	1.3%
Total	150	100.0%

FIGURE1: AGE WISE DISTRIBUTION OF SUBJECTS (PIE CHART)



AS SHOWN IN TABLE 1 AND FIGURE 1-

1. Majority of the enrolled subjects 63.3% were >25 years and above.
2. One third of the study subjects (35.3 %) were < 25 years of age.
3. Very few were beyond 35 years of age (1.3%).

TABLE 2: ASSOCIATION OF AGE WITH PRE-ECLAMPSIA (using Chi square test)

		DEVELOPMENT OF PE				Total	Chi-square value	p-value
		No		Yes				
Age group	< 25	46	35.7%	7	33.3%	53	2.267	0.453
	26-30	58	45.0%	8	38.1%	66		
	31-35	24	18.6%	5	23.8%	29		
	> 35	1	0.8%	1	4.8%	2		
TOTAL		129	100%	21	100%	150		

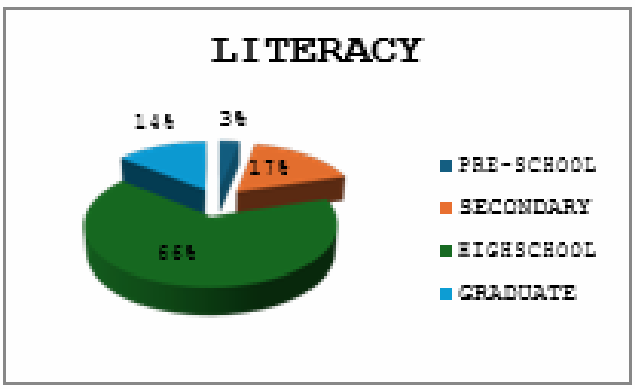
As shown in above table 2:

1. No statistically significant association between Age and Development of Pre-eclampsia was noted in our study using the Chi square test (Chi square value =2.26; p-value =0.45)

TABLE 3: LITERACY WISE DISTRIBUTION OF SUBJECTS.

LITERACY	No. of Cases	Percentage
PRE	4	2.7%
SECONDARY	22	14.7%
HIGH	85	56.7%
GRADUATE	18	12.0%
Total	150	100.0%

FIGURE 2: LITERACY WISE DISTRIBUTION OF SUBJECTS (PIE CHART)



AS SHOWN IN TABLE 3 and Figure 2:

1. Almost Half the subjects in our study (56.7%) had High School education.
2. (14. 7%) of subjects had secondary school education and 12% were Graduates.
3. Very few (2.7%) had only primary school education.

TABLE 4: ASSOCIATION OF LITERACY WITH PRE-ECLAMPSIA (using Chi Square test)

		Development of PE				Total	Chi-Square Value	P-Value
		No		Yes				
Literacy	Pre	4	3.1%	0	0.0%	4	0.819	0.845
	Secondary	22	17.1%	3	14.3%	25		
	High	85	65.9%	15	71.4%	100		
	Graduate	18	14.0%	3	14.3%	21		
Total		129	100%	21	100%	150		

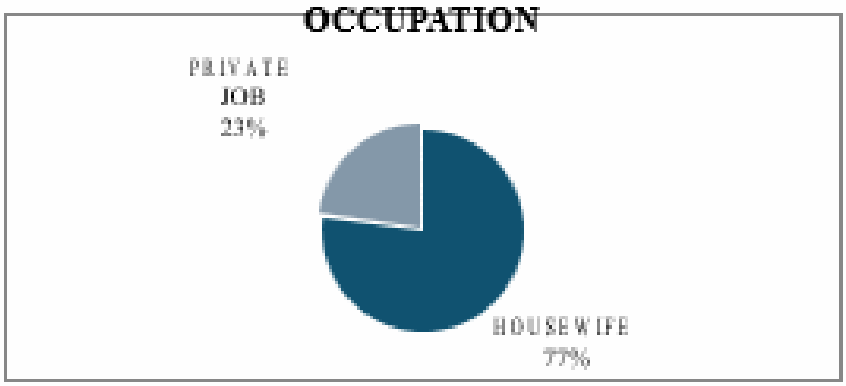
As shown in above table 4:

1. No statistically significant association between literacy And Development of Preeclampsia in our study using chi square test (chi square value- 0.819 and p-value =0.845).

TABLE 5: DISTRIBUTION OF SUBJECTS BY TYPE OF OCCUPATION.

TYPE OF OCCUPATION	No. of Cases	Percentage
HOUSEWIFE	116	77.3%
PRIVATE JOB	34	22.7%
TOTAL	150	100.0%

FIGURE 3: OCCUPATION WISE DISTRIBUTION OF SUBJECTS (PIE CHART)



As shown in above table 5 and figure 3

1. Majority of subjects (77.3%) in our study were housewives.
2. One fourth of our subjects (22.7%) were employed in factories and worked as semiskilled labourers.

TABLE 6: ASSOCIATION OF OCCUPATION WITH PRE-ECLAMPSIA (using Chi-square test).

		Development of PE				Total	Chi-Square	p-value
		No		Yes				
Occupation	Housewife	100	77.5%	16	76.2%	116	0.018	0.893
	Private	29	22.5%	5	23.8%	34		
Total	Job	129	100%	21	100%	150		

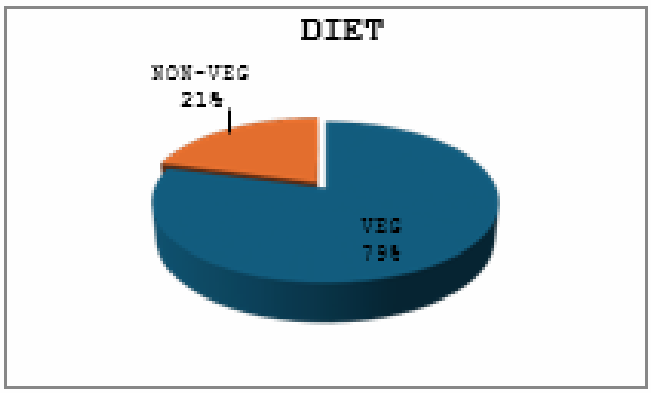
As shown in above table 6:

1. No statistically significant association between Occupation and Development of Preeclampsia was noted in our study using chi-square test (chi square value -0.018 and p-value =0.893).

TABLE 7: DISTRIBUTION OF SUBJECTS BY DIET.

Diet	No. of Cases	Percentage
NON-VEG	31	20.7%
VEG	119	79.3%
Total	150	100.0%

FIGURE 4: DIET WISE DISTRIBUTION OF SUBJECTS (PIE CHART).



As shown in the above table 7 and figure 4,

1. Majority of subjects (79%) were Vegetarians in our study.
2. Only One fifth of subjects (21%) were non-vegetarians in our study.

TABLE 8: ASSOCIATION OF DIET WITH PRE-ECLAMPSIA (using Chi-square test).

		Development of PE				Total	Chi-Square	p-value
		No		Yes				
Diet	Non-veg	27	20.9%	4	19.0%	31	0.039	0.843
	Veg	102	79.1%	17	81.0%	119		
Total		129	100.0%	21	100.0%	150		

As shown in above Table 8:

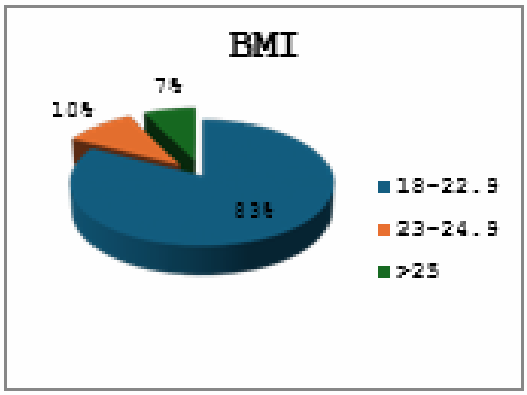
1. No statistically significant association between Diet and Development of Pre-eclampsia was noted in our study using chi-square test (Chi-square value- 0.039 and p-value= 0.843).

TABLE 9: DISTRIBUTION OF SUBJECTS BY BMI.

	BMI	Number of subjects	Percentage
BMI(kg/m2 body surface area)	18-22.9*	124	83%
	23-24.9**	15	10%
	25-30***	11	7%
Total		150	100%

*-Normal weight, **-Over-weight, ***Obese
*ASIA PACIFIC BMI classification of obesity By WHO (2000)[T2].

FIGURE 5: DISTRIBUTION OF SUBJECTS By BMI (PIE CHART).



As shown in the above Table 9 and Figure 5:

1. Majority of subjects (83%) in our study were in the Normal weight category (BMI 18-22.9 Kg/m2).
2. 10% of subjects were overweight.
3. Only 7% of the subjects were obese.

TABLE 10: GROUPWISE DISTRIBUTION BY MEAN BMI (KG/MF) IN NORMOTENSIVE AND PRE-ECLAMPTIC GROUPS (USING MANN-WHITNEY U TEST)

	Development of Preeclampsia				Z	p-value
	No		Yes			
BMI (KG/MF)	MEAN	SD	MEAN	SD	-5.661	**0.001**
	20.99	1.56	23.22	2.29		

(Mann-Whitney U test)

As shown in above table 10:

1. The mean BMI of subjects who develop preeclampsia was higher (23.22±2.29 kg/m^2) than the mean BMI of normotensive group (20.99±1.56 kg/m^2) and the difference was statistically significant with Z -5.661 and **p-value=0.001.**

TABLE 11: ASSOCIATION OF BMI WITH PRE-ECLAMPSIA (USING CHI-SQUARE TEST).

		Development of PE				Total	Chi-Square	p-value
		No		Yes				
BMI (kg/m^2)	18-22.9	116	89.9%	8	38.1%	124	36.8	**0.001**
	23-24.9	9	7.0%	6	28.6%	15		
	> 25	4	3.1%	7	33.3%	11		
Total		129	100%	21	100%	150		

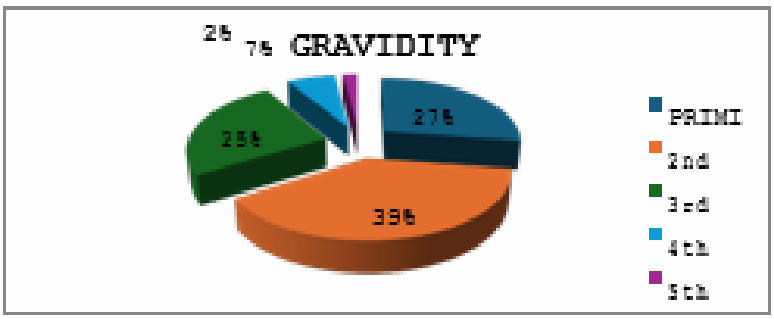
As shown in above table 11:

1. Amongst subjects who did not develop PE, majority (89%) were in the normal weight category.
2. Amongst the subjects who developed PE, the majority (61.9%) were either overweight or obese with 28.6% in the overweight category and 33.3% in the obese category.
3. A statistically significant association of BMI with Preeclampsia was noted in our study using chi square test (chi-square value – 36.8 and **p-value = 0.001**).

TABLE 12: DISTRIBUTION OF SUBJECTS BY GRAVIDITY.

Gravida	No. of cases	Percentage
PRIMI	41	27.3%
2	58	38.7%
3	38	25.3%
4	10	6.7%
5	3	2.0%
Total	150	100.0%

FIGURE 6: DISTRIBUTION OF SUBJECTS BY GRAVIDITY (PIE CHART).



As shown in above table 12 and figure 6:

1. The majority (72.7%) of subjects in our study were Multigravida.
2. One fourth (27%) of subjects were Primigravida.

TABLE 13: ASSOCIATION OF GRAVIDITY WITH PRE-ECLAMPSIA (using Chi-square test).

		Development of PE				Total	Chi-Square	p-value
		No		Yes				
Gravidity	PRIMI	33	25.6%	8	38.1%	41	1.858	0.762
	2	51	39.5%	7	33.3%	58		
	3	33	25.6%	5	23.8%	38		
	4	9	7.0%	1	4.8%	10		
	5	3	2.3%	0	0.0%	3		
Total		129	100.0%	21	100.0%	150		

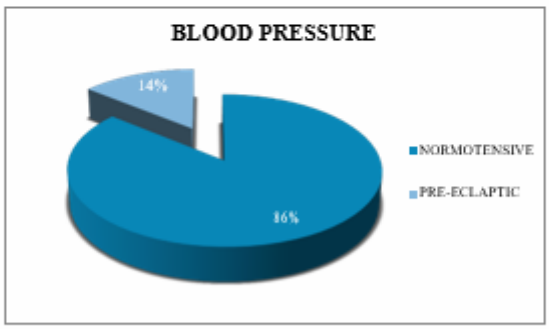
As shown in above table 13:

1. No statistically significant association between Gravidity and Development of Pre-eclampsia was noted in our study using chi-square test (chi-square value-1.858 and p-value =0.762).

TABLE 14: DISTRIBUTION OF SUBJECTS BASED ON DEVELOPMENT OF PRE-ECLAMPSIA.

Development of PE	No. of cases	Percentage
NO (NORMOTENSIVE)	129	86.0%
YES (PRE-ECLAMPTIC)	21	14.0%
TOTAL	150	100.0%

FIGURE 7: DISTRIBUTION OF SUBJECTS BASED ON DEVELOPMENT OF PRE-ECLAMPSIA (PIE CHART).



As shown in Above table 14 and figure 7,

1. In our study 14% of subjects developed pre-eclampsia.
2. 86% of subjects remained Normotensive.

TABLE 15: GROUPWISE MEANS OF PERIOD OF GESTATION AND B.P (SYSTOLIC AND DIASTOLIC) AT RECRUITMENT (16-24WEEKS) AMONGST THE NORMOTENSIVE AND PREECLAMPTIC SUBJECTS.

	DEVELOPMENT OF PE				Z	p-value
AT RECRUITMENT	No		Yes			
	Mean	SD	Mean	SD		
POG (weeks)	20.20	2.55	20.00	2.41	0.338	0.735
SYSTOLIC BP (mmHg)	119.86	6.40	121.62	4.50	-1.210	0.228
DIASTOLIC BP (mmHg)	74.79	6.31	74.76	5.35	0.020	0.984

(Mann-Whitney U test)

As shown in the above table 15 using Mann-Whitney U test:

1. The mean POG in Normotensive and Preeclamptic group was 20.20±2.55 weeks and 20±2.41 weeks respectively and was similar and comparable with no statistically significant difference with z-value- 0.338 and p-value= 0.735.
2. The mean SBP in Normotensive and Preeclamptic group were 119.86±6.40 mm of Hg and 121.62±4.50 mm of Hg respectively and was similar and comparable with no statistically significant difference in SBP values with z value -1.210 and p-value =0.228.
3. The mean DBP in Normotensive and Preeclamptic group were 74.79±6.31 mm of Hg and 74.76±5.35 mm of Hg respectively and also noted to be similar and comparable with no statistical significance with z-value 0.020 and p-value= 0.984.

TABLE 16: TRIMESTER WISE DISTRIBUTION BY MEANS OF SBP AND DBP AFTER RECRUITMENT at 24-32 WEEKS & >32 WEEKS POG AMONGST THE NORMOTENSIVE AND PREECLAMPTIC GROUPS.

Blood Pressure After Recruitment	Normotensive		Pre-Eclamptic		Z	p-value
	Mean	SD	Mean	SD		
SB. P (24-32 WEEKS)	119.63	7.07	123.24	5.16	-2.243	**0.026**
DB. P (24-32 WEEKS)	77.96	6.25	74.57	5.10	0.248	0.805
SB. P >32 weeks	121.05	6.97	145.24	7.79	-14.510	**0.000**
DB. P >32weeks	72.93	5.86	95.67	6.54	-16.218	**0.000**

(Mann-Whitney U test)

As shown in above table 16:

1. The mean Systolic B.P from 24-32 weeks POG in Preeclamptic group was higher (123.24±5.16 mm of Hg) than in the normotensive group (119.63±7.07 mm of Hg) and the difference was statistically significant with **p-value=0.026**.
2. The mean Diastolic B.P from 24-32 weeks POG in Preeclamptic group was 74.57±5.10 mm of Hg and in the normotensive group was 77.96±6.25 mm of Hg and the difference was not statistically significant with p-value=0.805.
3. The mean of Systolic B.P after 32 weeks POG in Preeclamptic group was significantly higher (145.24±7.79 mm of Hg) as compared to Normotensive group (121.05±6.97 mm of Hg) and the difference was found to be statistically significant (**p-value <0.05**).
4. The mean of Diastolic BP after 32 weeks POG in Preeclamptic group was significantly higher (95.67±6.54 mm of Hg) as compared Normotensive group (72.93±5.86 mm of Hg) and the difference was found to be statistically significant (**p-value <0.05**).

TABLE 17: GROUPWISE DISTRIBUTION OF MEANS OF ABSOLUTE NEUTROPHILS/LYMPHOCYES AND PLATELET COUNTS IN NORMOTENSIVE AND PRE-ECLAMPTIC GROUPS.

	Normotensive		Preeclamptic		Z	p-value
	Mean	SD	Mean	SD		
Absolute neutrophil counts (10^3/µL)	5.53	1.04	6.54	1.67	-3.78	0.000
Absolute lymphocyte counts (10^3/µL)	1.81	0.46	1.86	0.47	-0.45	0.650
Platelet counts (10^3/µL)	198.51	74.42	228.76	78.93	-1.71	0.089

(Mann-Whitney U test)

The above table 17, shows the distribution of absolute Neutrophils, Lymphocytes and platelet counts amongst the Normotensive(N) vis-a vis Pre-eclamptic (PE) group (using Mann-Whitney U test).

1. The mean Absolute neutrophils (10^3/µL) in the Normotensive and preeclamptic group was 5.53±1.04 and 6.54±1.67 respectively and the mean difference in the two groups was statistically significant (Z value -3.78 and **p-value = 0.000**).
2. The mean Absolute lymphocytes (10^3/µL) in Normotensive and PE group was 1.81±0.46 and 1.86±0.47 respectively. There was no statistically significant difference in the mean values in the two groups with Z value -0.45 and p-value= 0.650.
3. However, a higher platelet count (10^3/µL) was noted in the PE group (228.76±78.93) compared to the normotensive group (198.51±74.42) but the difference was statistically non-significant with Z value -1.71 and p-value= 0.089.

TABLE 18: GROUPWISE DISTRIBUTION OF MEANS OF INFLAMMATORY MARKERS (NLR, PLR AND MPV) IN NORMOTENSIVE AND PRE-ECLAMPTIC GROUPS.

Inflammatory Markers	Normotensive(N)		Pre-Eclamptic(PE)		Z	p-value
	Mean	SD	Mean	SD		
N/L Ratio	3.25	0.95	3.65	1.06	-1.748	0.083
P/L Ratio	101.12	25.64	125.63	49.55	-3.471	**0.001**
MPV (fL)	11.83	2.04	12.01	1.95	-0.393	0.695

(Mann-Whitney U test)

The above table 18 shows the distribution of various Inflammatory markers (NLR, PLR, MPV) amongst the Normotensive(N) vis-a vis Pre-eclamptic (PE) group (using Mann-Whitney U test).

1. The mean NLR in the Normotensive and preeclamptic group was 3.25±0.95 and 3.65±1.06 respectively. However, there was no statistically significant difference in the means of NLR amongst the two groups (Z value -1.748 and p-value = 0.083).
2. The mean of MPV in Normotensive and PE group was 11.83±2.04 fL and 12.01±1.95 fL respectively. There was no statistically significant difference in the mean MPV in the two groups with Z value -0.393 and p-value= 0.695.
3. However, a higher mean PLR was noted in the PE group (125.63±49.55) compared to the normotensive group (101.12±25.64) and the difference was statistically significant with Z value -3.471 and **p-value= 0.001**.

TABLE 19: SPEARMAN'S rho CORRELATIONS OF INFLAMMATORY MARKERS (NLR/PLR/MPV).

Spearman's rho	Correlations	P/L Ratio	MPV(FL)
N/L Ratio	Correlation Coefficient	0.323	0.124
	p-value	**0.000**	0.129
	N	150	150
P/L Ratio	Correlation Coefficient		-0.178
	p-		value
	N		0.029 150

(Spearman's rho)

As shown in the above table 19 using Spearman's rho correlation:

1. A statistically significant positive correlation was noted between NLR with PLR with correlation coefficient 0.323 And p-value =0.000.

2. However, a Negative correlation of PLR with MPV was noted, with a correlation coefficient -0.178 and p-value 0.029 which also found to be statistically significant.

TABLE 20: PREDICTION OF PREECLAMPSIA USING AUC.

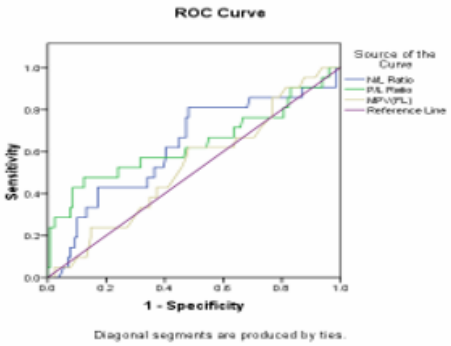
Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	p-value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Absolute Neutrophils (10^9/ µL)	0.67	0.08	**0.013**	0.52	0.82
Absolute Lymphocytes (10^9/ µL)	0.52	0.07	0.751	0.39	0.65
Platelet Counts (10^9/µL)	0.63	0.06	0.061	0.51	0.75
N/L Ratio	0.625	0.068	0.066	0.492	0.759
P/L Ratio	0.635	0.079	**0.047**	0.481	0.790
MPV (fL)	0.529	0.066	0.671	0.400	0.658

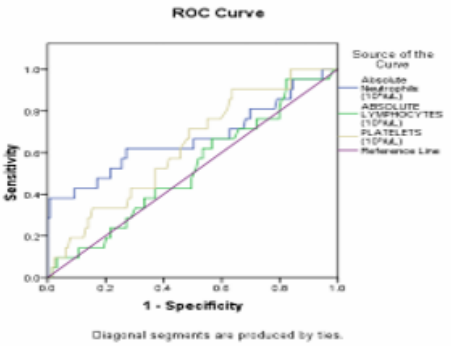
TABLE 21: PREDICTION OF PREECLAMPSIA USING (COORDINATES OF THE CURVE).

Coordinates of the Curve								
Test Result Variable(s)	Positive if Greater Than or Equal To	Sensitivity	1 - Specificity	Specificity	PPV (%)	NPV (%)	Accuracy (%)	Youden Index
Absolute Neutrophils (10^9/µL)	7.23	39.13%	0.82%	99.22%	90%	90.14%	90.13%	0.373
Absolute Lymphocytes (10^9/µL)	1.38	95.24%	82.2%	17.83%	15.87%	95.83%	28.67%	0.131
Platelet Counts (10^9/µL)	164.00	90.48%	63.6%	36.43%	18.81%	95.92%	44.00%	0.269
NLR	3.06	80.95%	48.1%	51.94%	21.52%	94.37%	56%	0.329
PLR	127.80	47.62%	12.4%	87.60%	38.46%	91.13%	82%	0.352
MPV (fL)	11.75	61.90%	48.1%	51.94%	17.33%	89.33%	53.33%	0.138

(PPV-POSITIVE PREDICTIVE VALUE; NPV-NEGATIVE PREDCITIVE VALUE; NLR-NEUTROPHIL-LYMPHOCYTE RATIO; PLR-PLATELET TO LYMPHOCYTE RATIO; MPV- MEAN PLATELET VOLUME)

FIGURE 8 & 9: PREDICTION OF PREECLAMPSIA USING ROC CURVE.





As shown in Table 20, 21 and Fig 8 & 9 ROC curve analysis with AUC for various inflammatory markers (Absolute Neutrophil count, Absolute lymphocyte count, Platelet counts, NLR, PLR and MPV) in second trimester (16-24 weeks) of pregnancy for prediction of PE was done and following was observed:

1. Using Absolute neutrophil counts at optimal cut off 7.23 x10³/µL in ROC curve analysis showed an AUC of 0.67 (95% CI 0.52-0.82) with SE 0.08, **p value=0.013**(significant) was noted. This had a sensitivity of 39.13%, specificity 99.22%, false positive rate of 0.82% with Positive predictive value (PPV) of 90% and Negative predictive value (NPV) of 90.14% with an accuracy of 90.13%.
2. Absolute lymphocyte counts at optimal cut-off 1.38 x10³/µL in the ROC curve analysis showed an AUC of 0.52 (95% CI 0.39-0.65, p-value=0.751) with SE 0.07. This had a sensitivity 95.24%, specificity 17.83%, false positive rate 82.2% with PPV of 15.87% and NPV of 95.83% with an accuracy of 28.67%.
3. Platelet counts at an optimal cut-off 164 x10³/µL in the ROC curve analysis showed an AUC of 0.63 (95% CI 0.51-0.75, p-value=0.061near to significant) with SE 0.06. This had a sensitivity 90.48%, specificity 36.43%, false positive rate 63.6% with PPV of 18.81% and NPV of 95.92% with an accuracy of 44.00%.
4. Neutrophil-lymphocyte ratio at optimal cut-off 3.06 in the ROC curve analysis showed an AUC of 0.625 (95% CI 0.492-0.759, p-value=0.066 near to significant) with SE 0.068. This had a sensitivity 80.95%, specificity 51.94%, false positive rate 48.1% with PPV of 21.52% and NPV of 94.37% with an accuracy of 56%.
5. Platelet-lymphocyte ratio at optimal cut-off 127.80 in the ROC curve analysis showed an AUC of 0.635 (95% CI 0.481-0.790, **p-value=0.047** significant) with SE 0.079. This had a sensitivity 47.62%, specificity 87.60%, false positive rate 12.4% with PPV of 38.46% and NPV of 91.13% with an accuracy of 82%.
6. Mean platelet volume at optimal cut-off 11.75 fL in the ROC curve analysis showed an AUC of 0.529 (95% CI 0.400-0.658, p-value=0.671 non-significant) with SE 0.066. This had a sensitivity 61.90%, specificity 51.94%, false positive rate 48.1% with PPV of 17.33% and NPV of 89.33% with an accuracy of 53.33%.

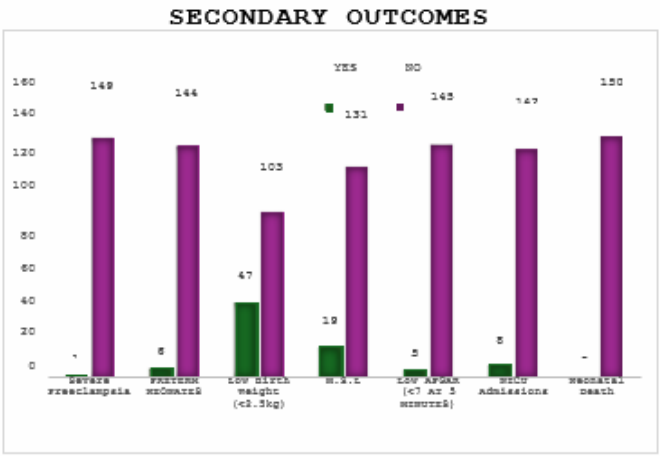
TABLE 22: PREDICTION OF PREECLAMPSIA USING NLR/PLR/MPV USING ODDS RATIO.

INFLAMMATORY MARKERS	p-value	odd ratio	95% C.I for odd ratio	
			Lower	Upper
NL Ratio	0.738	1.092	0.652	1.830
PL Ratio	**0.005**	1.024	1.007	1.041
MPV (fL)	0.286	1.158	0.885	1.515

As shown in above table 22,

1. PLR had an odds ratio = 1.024 in the prediction of pre-eclampsia which was statistically significant with **p-value= 0.005**.
2. However, the NLR and MPV were not found to be effective predictors of pre-eclampsia using odds ratio with value of 1.092 and 1.158 respectively with p-value =0.738 and p-value=0.286 respectively which was not statistically significant.

FIG 10: DISTRIBUTION BY SECONDARY OBJECTIVES IN OUR STUDY.



(x-axis = outcomes, y-axis= number of subjects)

TABLE 23: DISTRIBUTION BY SECONDARY OBJECTIVES IN OUR STUDY.

Secondary Objectives	No		yes		Total
	No. of Cases	Percentage	No. of Cases	Percentage	
Severe preeclampsia	149	99.3%	1	0.7%	150 (100%)
Preterm delivery	144	96%	6	4%	150 (100%)
Low Birth weight (<2.5kg)	103	68.6%	47	31.3%	150 (100%)
Meconium stained liquor (MSL)	131	87.3%	19	12.7%	150 (100%)
Low APGAR (<7 at 5 minutes)	145	96.7%	5	3.3%	150 (100%)
NICU Admission	142	94.7%	8	5.3%	150 (100%)
Neonatal death	150	100%	0	0%	150 (100%)

As shown in the above Table 23, fig 10.

1. We noted that out total 150 subjects only 1(1%) subject developed severe preeclampsia. We also noted 21 (14%) subjects developed PE and out of which only 1 developed preeclampsia with severe features.
2. Out of 150 deliveries 6 (4%) were preterm and 144 (96%) were term deliveries.
3. We noted that out of 150 deliveries 47 (31.3%) were low birth weight (<2.5kg) and 103 (68.6%) were of normal weight(>2.5kg).
4. Majority 131 (87.3%) deliveries were with clear liquor and 19 (12.7%) were MSL.
5. Only 5 (3.3%) deliveries had a low APGAR (<7 at 5 min) and 145 (96.7%) were of normal APGAR score.
6. 8 (5.3%) delivered babies were shifted to NICU and 142 (95.7%) were shifted to mother side.
7. In our study we noted zero neonatal deaths.

TABLE 24: ASSOCIATIONOF INFLAMMATORY MARKERS (NLR, PLR AND MPV) WITH PRETERM DELIVERIES.

Inflammatory Markers	Preterm Delivery				Z	p-value
	No		Yes			
	Mean	SD	Mean	SD		
N/L Ratio	3.30	0.99	3.41	0.50	-0.258	0.797
P/L Ratio	104.31	31.29	110.37	27.76	-0.466	0.642
MPV (fL)	11.89	2.01	11.00	2.09	1.058	0.292

(MANN-WHITNEY U TEST)

As shown in the above table 24 (using Mann-Whitney U test):

1. The mean NLR in subjects with Preterm delivery was slightly higher than those delivering at term with the mean values of 3.41±0.50 in preterm group vis a vis 3.30±0.99 in term group. However, the difference in mean NLRs amongst the two groups was not found to be statistically significant with z value= -0.258 and p-value =0.797.
2. The mean PLR in subjects of Preterm deliveries was higher than in those delivering at term with mean values of 110.37±27.76 in preterm group versus 104.31±31.29 in the term group. However, the difference in means was not statistically significant with z value= -0.466 and p value=0.642.
3. The mean MPV in both group preterm vis-à-vis term deliveries 11±2.09 fL and 11.89±2.01fL respectively. The difference was also noted to statistically non-significant with z value= 1.058 and p-value=0.292.

TABLE 25: ASSOCIATIONOF INFLAMMATORY MARKERS (NLR, PLR AND MPV) WITH FETAL BIRTH WEIGHT.

Inflammatory Markers	Fetal Birth Weight(FBW)				Z	p-value
	< 2.5 KG (LBW)		> 2.5 KG			
	Mean	SD	Mean	SD		
N/L Ratio	3.43	1.02	3.25	0.96	1.008	0.315
P/L Ratio	108.00	35.95	102.98	28.67	0.916	0.361
MPV (fL)	11.70	1.91	11.92	2.07	-0.627	0.531

(MANN-WHITNEY U TEST)

As shown in the above table 25 using Mann-Whitney U test:

1. The mean NLR in both groups, i: e LBW <2.5kg and those with normal birth weight was 3.43±1.02 and 3.25±0.96 respectively and the difference was not statistically significant (z value=1.008 and p-value=0.315).
2. The mean PLR in LBW and normal birth weight groups was 108±35.95 and 102.98±28.67 respectively. The difference was not statistically significant (z value= 0.916, p-value= 0.361).
3. The mean MPV in LBW group (<2.5kg) and normal weight (>2.5kg) was 11.70±1.91 fL and 11.92±2.07 fL respectively and the difference was not statistically significant (z value= -0.627 and p-value=0.531).

TABLE 26: ASSOCIATION OF INFLAMMATORY MARKERS (NLR, PLR AND MPV) WITH OLIGOHYDROMNIOS (AFI<5cm).

Inflammatory Markers	Development of Oligohydramnios				Z	p-value
	No(N=135)		Yes(N=15)			
	Mean	SD	Mean	SD		
N/L Ratio	3.35	0.99	2.91	0.80	1.678	0.095
P/L Ratio	104.40	31.09	105.98	32.20	-0.187	0.852
MPV (fL)	11.81	2.03	12.21	1.95	-0.714	0.477

(MANN-WHITNEY U TEST)

As shown in the above table 26 using Mann-Whitney U test:

1. Out of 150 subject's oligohydramnios AFI <5cm was noted in 15 subjects (10%) while majority 135 (90%) had normal liquor.
2. The mean NLR in both the groups of subjects with oligohydramnios and those with normal liquor was 2.91±0.80 and 3.35±0.99 respectively. The difference in the NLR means in the two groups was not statistically significant (z value =1.678 and p-value= 0.095).
3. The mean PLR in both the groups of subjects with oligohydramnios and those with normal liquor was 105.98±32.20 and 104.40±31.09 respectively. The difference in means of PLR was not statistically significant, with z-value =0.187 and p-value =0.852.
4. The mean MPV in both the groups of subjects with oligohydramnios and those with normal liquor was 12.21±1.95 fL and 11.81±2.03 fL respectively. The difference was found to have no statistical significance with z value= -0.714 and p-value= 0.477.

TABLE 27: ASSOCIATIONOF INFLAMMATORY MARKERS (NLR, PLR AND MPV) WITH MECONIUM STAINED LIQUOR.

Inflammatory Markers	Meconium Stained Liquor				Z	p-value
	No		Yes			
	Mean	SD	Mean	SD		
N/L Ratio	3.31	0.99	3.29	0.92	0.078	0.938
P/L Ratio	102.85	28.80	116.30	42.97	-1.774	0.078
MPV (fL)	11.90	2.05	11.51	1.76	0.791	0.430

(MANN-WHITNEY TEST)

As shown in the above table 27 using Mann-Whitney U test:

1. The mean NLR in both the groups of subjects with Meconium Stained Liquor and those with clear liquor was 3.29±0.92 and 3.31±0.99 respectively. The difference in the NLR means in the two groups was not statistically significant (z value= 0.078 and p-value= 0.938).
2. The mean PLR in both the groups of subjects with Meconium stained Liquor and those with clear liquor was 116.30±42.97 and 102.85±28.80 respectively. The difference in means of PLR on Mann Whitney test was not statistically significant, with z-value =-1.774 and p-value =0.078.
3. The mean MPV in both the groups of subjects with Meconium Stained Liquor and those with clear liquor was 11.51±1.76 fL and 11.90±2.05 fL respectively. The difference was found to have no statistical significance using Mann Whitney with z value= 0.791 and p-value =0.430.

TABLE 28: ASSOCIATIONOF INFLAMMATORY MARKERS (NLR, PLR AND MPV) WITH LOW APGAR SCORE (<7 At 5 Minutes).

Inflammatory Markers	A.P.G.A.R(AT 5MIN)				Z	p-value
	< 7 at 5 minutes		≥ 7 at 5 minutes			
	Mean	SD	Mean	SD		
N/L Ratio	2.77	1.05	3.33	0.97	-1.264	0.208
P/L Ratio	103.88	27.86	104.58	31.29	-0.049	0.961
MPV (fL)	12.14	1.97	11.84	2.03	0.322	0.748

(MANN-WHITNEY U Test)

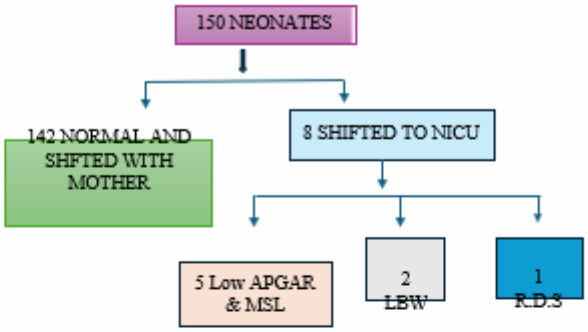
As shown in the above table 28:

1. The mean NLR in both the groups of subjects with Low APGAR score (<7 at 5minutes) and those with Normal APGAR score (≥7 at 5 minutes) was 2.77±1.05 and 3.33±0.97 respectively. The difference in mean NLRs amongst the two groups was not found to be statistically significant with z value= -1.264 and p-value=0.208 using Mann-Whitney U test.
2. The mean PLR in both the groups of subjects with Low APGAR score and those with Normal APGAR score was 103.88±27.86 and 104.58±31.29 respectively. The difference in means of PLR on Mann Whitney test was not statistically significant, with z-value =-0.049 and p-value =0.961.
3. The mean MPV in both the groups of subjects with Low APGAR score and those with Normal APGAR score was 12.14±1.97 fL and 11.84±2.03 fL respectively. The difference was found to have no statistical significance using Mann Whitney U test with z value =0.322 and p-value= 0.748.

TABLE 29: ASSOCIATION OF INFLAMMATORY MARKERS (NLR, PLR AND MPV) WITH NICU ADMISSIONS.

Inflammatory Markers	NICU ADMISSION				Z	p-value
	No		Yes			
	Mean	SD	Mean	SD		
N/L Ratio	3.33	0.98	2.91	0.86	1.178	0.241
P/L Ratio	104.64	31.53	103.13	23.62	0.133	0.895
MPV (fL)	11.83	2.03	12.28	1.79	-0.606	0.545

FIG: 11 DISTRIBUTION OF NEONATES ADMITTED TO NICU.



As shown in the above table 29 & Fig 10:

1. Out of 150 neonates 8 neonates were shifted to NICU and 142 normal neonates were shifted with mother. Out of 8 neonates 5 had Low APGAR along with MSL, 2 were LBW and 1 had respiratory distress syndrome (RDS).
2. The mean NLR in subjects with normal neonate's vis a vis those with neonates needing NICU admissions was, 2.91±0.86 and 3.33±0.98 respectively. The difference in the NLR means in the two groups was not statistically significant on Mann-Whitney U test (z value= 1.178 and p-value= 0.241).
3. The mean PLR in the groups of subjects with normal neonate's vis a vis those requiring NICU admissions was, 104.64±31.53 and 103.13±23.62 respectively. The difference in means of PLR in the two groups was not statistically significant using Mann-Whitney U test (z-value =0.133 and p-value =0.895).
4. The mean MPV in subjects with normal neonates and in those requiring NICU admission was 11.83±2.03 fL and 12.28±1.79 fL respectively. The difference in the mean MPV in the two groups was not statistically significant on Mann-Whitney U test (z value= -0.606 and p-value =0.545).

DISCUSSION

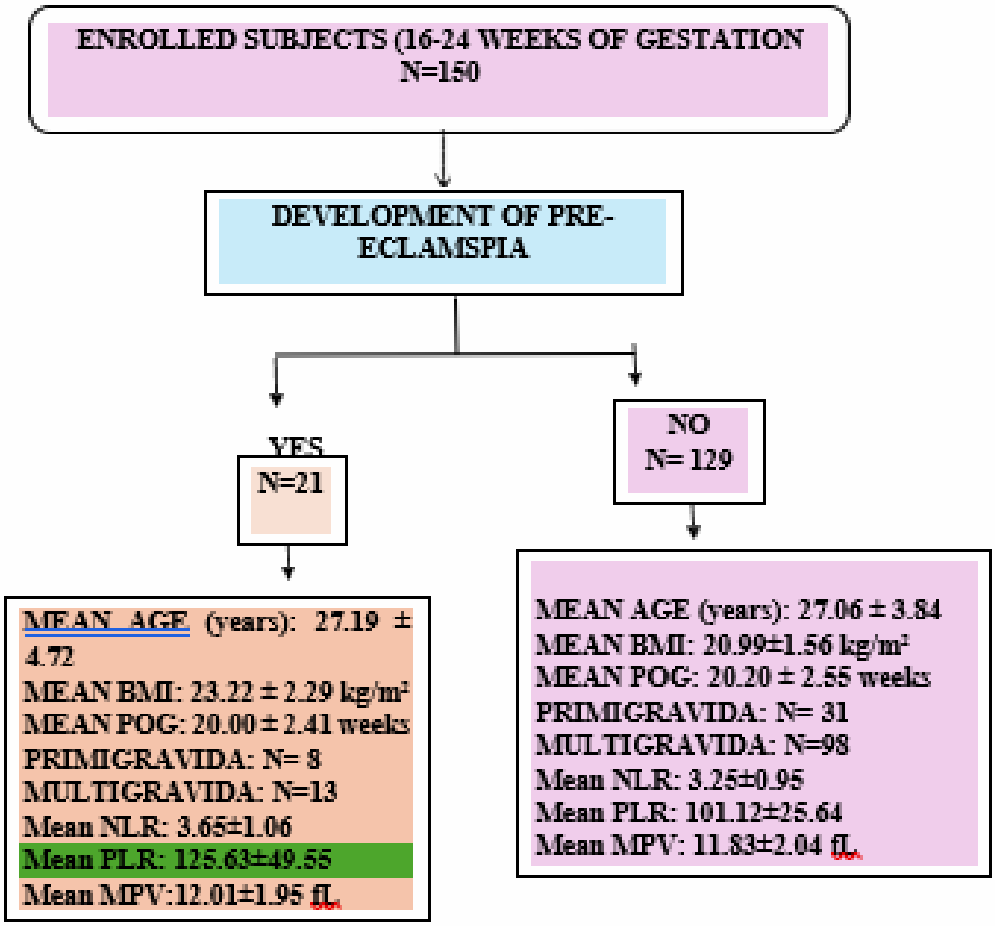
Preeclampsia represents a hypertensive disorder exclusive to pregnancy, raising significant clinical concerns due to its potential to induce severe fetal and maternal complications, including eclampsia, HELLP syndrome, pulmonary edema, congestive heart failure, acute renal failure, placental abruption, and stillbirth. The disorder presents a considerable challenge to obstetricians due to its complex clinical manifestation and the differential involvement of multiple organ systems to varying extents. Despite ongoing research and the development of novel serological biomarkers, in conjunction with inflammatory markers like NLR, PLR AND MPV for predictive purposes, a singularly reliable predictor of preeclampsia remains unidentified.

Our study aimed to investigate the prediction of preeclampsia and its severity using inflammatory markers like neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) during the second trimester (16-24 weeks) of pregnancy. This was a prospective observational study on 150 participants aged 18-37 years with a BMI of 18.5 to 30 kg/m^2. Blood samples were collected for inflammatory markers upon enrollment after informed consent for participation in the study. Participants were monitored until delivery, with data collected on systolic and diastolic blood pressure, fetal growth and maternal complications, Birth weight, neonatal outcomes, including preterm deliveries, meconium-stained liquor (MSL), low Apgar scores, NICU admissions, and other complications, which were also recorded. All participants completed the study and were included in the final analysis.

Out of 150 participants in our study, 21(14%) developed Pre-eclampsia (PE) in the third trimester of pregnancy, and 129(86%) remained normotensive throughout pregnancy till delivery including the postpartum period. In our we had only 1 case of severe preeclampsia (Refer Table-14, fig:7). The subjects were divided into two groups: the Preeclamptic group and Normotensive group for statistical analysis.

Following is the summarised consort flow diagram of this study:

FIG 12: CONSORT FLOW DIAGRAM



AGE

In our study the mean age of study participants was 27.19±4.72 years in PE group and 27.06±3.84 years in normotensive group. No significant association of age with PE was noted in our study using chi-square analysis (Refer Table 1, 2 & fig: 1). The mean age in our study was similar to that reported by **Cintesun et al.** (2018) [61] with age group of 28 and 29 years in PE and Non-PE groups respectively, **Oglak et al (2021)** [73] with 28.3 and 27.4 years in PE and Non-PE groups respectively.

LITERACY

In our study, maternal literacy levels were similar in both the Preeclamptic and normotensive group. We did not note any statistically significant association of literacy with PE (Refer to tables 3, 4& fig:2). Contrary to our observation the study conducted by **Tebeu et al. (2011)** [74] reported that illiterate women had a higher likelihood of developing PE.

OCCUPATION

In our study, a majority (77.3%) of subjects were housewives. In both the normotensive and preeclamptic groups. No significant association of preeclampsia with occupation was noted (refer to table 5,6 & fig:3). Similar to our observations **Tebeu et al.** (2011)[74] also reported no association of PE with occupation. However, contrary to our observation **Bilhartz et al.** (2013)[75] reported a higher risk of preeclampsia amongst working class women.

DIET

In our study, a substantial majority (79%) of the participants were vegetarians and 21% were non-vegetarians. The distribution of dietary habits was similar in the PE versus normotensive groups (refer Tables 7,8 & fig:4). Similar to our observation Study by **Singh et al** (2021)[76], also reported no statistically significant relation between the type of diet and hypertension in pregnancy.

BMI

Majority of subjects enrolled in our study were in the normal weight category (83%) (BMI-18-22.9 kg/m^2) whereas (10%) were overweight BMI: 23-24.9 kg/m^2 and 7% were obese as per the WHO standards of BMI for southeast Asian countries (refer to Tables 9 & fig:5)[72]. The mean Body Mass Index (BMI) was also significantly higher in the preeclamptic group (23.22±2.29 kg/m^2) as compared to normotensive group with BMI of (20.99±1.56 kg/m^2), **p=0.001** in our study (refer table 10). Our observations were comparable with study done by **Sachan et al.** (2017)[69] in the second trimester of pregnancy who also reported a significantly higher mean BMI in PE group (25.13±0.96 kg/m^2) as compared to BMI (22.10±0.52 kg/m^2) in normotensive group (**p=0.024**). The mean BMI in a study by **Manuaerts et al.** (2019)[42] was (23.60±3.66 kg/m^2) in the PE group which was similar to the mean BMI of (23.22±2.29 kg/m^2) in preeclamptic group in our study. However, these authors reported a higher mean BMI in normotensive group (22.69±3.12 kg/m^2) as compared to mean BMI (20.99±1.56 kg/m^2) in normotensive subjects as in our study which may have been due to different population groups. However contrary to our observation they did not find any statistically significant difference in the BMI between the two groups (p=0.13). **Bulbul et al.** (2021)[77] noted a significantly higher mean BMI in the preeclamptic (28.00±2.62 kg/m^2) compared to the normotensive group (26.73±2.97 kg/m^2) with **p<0.001** similar to our observation. However, the mean BMI values in this was much higher in both the groups compared to our study which may have been due to different populations studied. We also observed that amongst the subjects who did not

develop PE majority (89.9%) were in the normal weight category and amongst those who develop PE majority (61.9%) were either overweight or obese and we noted a statistically significant association of BMI with PE **p-0.001** (refer table 11). Our observations were similar to that reported by **Jalal p et al. (2016)**[78] who also reported excess body mass index is significantly associated with increased risk of PE.

GRAVIDITY

In our study, 72.7 % 0f subjects were multigravida and 27.3% were primigravida subjects (refer table 12 & fig:6). We did not observe any significant association of gravidity with PE using chi-square test (p=0.762) (refer table :13). Our observation is similar to that reported by **Oglak et al.** (2021) [46] and **Bulbul et al.** (2021) [77] who also noted no association of gravidity with PE. Contrary to our observation studies by **Reddy et al. (2019)** [43], **Mannaerts et al. (2019)** [42], **Daud et al. (2022)**[70] and **Cintesun et al. (2018)** [81] noted an association of PE with gravidity with higher risk of PE in primigravida's than multigravidas.

TRIMESTER WISE TRENDS OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN NORMOTENSIVE AND PRE ECLMAPTIC GROUPS.

In our study we noted Preeclampsia amongst 14% of the subjects while 86% subjects continued to remain normotensive throughout pregnancy till delivery with no cases of early onset Preeclampsia before 32 weeks of gestation (refer table 14, 15 & fig:7).

In our study we noted mean SBP (119.86±6.4 mmHg) and DBP of (74.79±6.3 mmHg) at the time of recruitment in the 2nd trimester amongst the subjects who continued to remain normotensive throughout pregnancy. At the time of recruitment, the mean SBP of 121.62±4.5 mmHg and DBP of 74.76±5.35 mmHg was noted amongst those subjects who later developed PE in our study (refer Table 15,16). There was no significant difference in systolic BP (P value 0.228) nor diastolic BP (p Value 0.984) at recruitment amongst subjects who later remained normotensive(normotensive group) or became preeclampsia (PE group) in our study Contrary to our observations **Mannaerts et al. (2019)**[42] in their study noted a significant difference in the systolic and diastolic BP at recruitment itself amongst the normotensive(SBP 118.67±12.78 mmHg , DBP 68.12±9.32 mmHg) and preeclamptic group (SBP 125.53±15.40 mmHg ,DBP 74.05±8.46 mmHg) at recruitment prior to 20 weeks of gestation (p Value 0.02 and 0.007 respectively).

After 24 weeks of gestation up to till 32 weeks all the recruited subjects continued to have SBP and DBP in normal range and none developed PE. There was no statistically significant difference in diastolic BP in the normotensive and PE group up to 32 weeks of gestation (p value (p value 0.805). However, till 32 weeks despite the Systolic BP continuing to remain in the normal range, we noted a significantly higher mean SBP in the preeclamptic group (123.24 ±5.16 mmHg) viz a viz mean SBP of (119.63 ±7.07 mmHg) in the normotensive group with **p value 0.026** (Refer to table 16).

After 32 weeks of gestation, we noted a rise in both SBP and DBP as per the criterion of diagnosing preeclampsia amongst the subjects of preeclamptic group. We noted a statistically significant increase in both the SBP & DBP in the preeclamptic women with SBP of 145.24±7.79 mmHg and DBP of 95.67±6.54 mmHg compared to normotensive women with SBP of 121.05±6.97 mmHg and DBP of 72.93±5.86 mmHg **(p value 0.000)** (Refer Table 16). Similar to our observations significantly higher SBP and DBP trends were reported in the preeclamptic group vis a vis normotensive groups in the various studies by **Jeon et al. (2017)**[55], **Sweed et al. (2021)**[35] **Singgih et al. (2021)** [58], **Sachan et al. (2017)**[59], **Gogoi et al. (2019)**[11].

THE TREND OF NEUTROPHILS, LYMPHOCYTES AND PLATELET COUNT IN OUR STUDY.

- **ABSOLUTE NEUTROPHILS(x10^3/µL)**: In our study we noted that at recruitment at 16-24 weeks gestation, the mean absolute neutrophil counts (x10^3/µL) were significantly higher 6.54±1.67 x10^3/µL amongst those subjects who later developed PE (PE group) vis a vis 5.53±1.04 x10^3/µL amongst those who remained normotensive (normotensive group**(p=0.000)** (refer table 17). Similar to our study **Sabry et al. 2024**[71] also reported a significantly higher mean absolute neutrophil count in PE group (6.8±1.6) compared to the normal pregnancy group. (4.5±1.1 x10^3/µL) and **(p=0.01).** However, this study was done in the third trimester and is not comparable to our study. **Wang et al. 2019**[12] also reported a significantly higher mean neutrophil counts in preeclamptic group (6.80±2.13 x10^3/µL) than in normotensive group (6.16±1.51 x10^3/µL) **p<0.01** but this study too was done in the third trimester of pregnancy unlike our study done in second trimester.

  Similarly **Oglak et al. (2021)** [46] in their study conducted in third trimester of pregnancy observed a significantly higher mean absolute neutrophil count in both mild and severe preeclampsia (PE) groups compared to the normotensive group, with values

of 8.2±3.1 x10^3/µL, 8.6±3.5 x10^3/µL, and 6.8±1.7 x10^3/µL, respectively. The differences were statistically significant, with **p=0.003** for the mild PE versus normotensive group and p<0.001 for the severe PE versus normotensive group. Although their study also showed an increase in neutrophil counts in the PE groups compared to normotensive group, the overall mean values of neutrophils were much higher in both the normotensive and preeclamptic groups compared to our study. This discrepancy may have been due to differences in the trimesters during which the studies were conducted and variations in the study populations compared to our study.

Contrary to our observations, **Cintesun et al. (2018)**[51] in their study done in third trimester of pregnancy found no statistically significant difference in mean neutrophils counts in the PE versus control groups (p=0.80). However, this study reported a higher mean absolute neutrophil count in both PE group (8.72) versus normotensive group (7.74) compared to our observation and this may have been due to populations differences. **Kim et al. (2018)**[49] also found no statistically significant difference in the mean absolute neutrophil counts in the PE 6.527±.0.20 x10^3/µL versus normotensive groups (6.554±0.124 x10^3/µL), p value =0.913. **Other authors Toptas et al. (2016)**[52], **Damar et al. (2022)**[48] and **Daud et al. (2022)**[70] have also reported no statistically significant difference in the mean absolute neutrophils between the PE group and the control group. Contrary to the role of neutrophils in the pathogenesis of PE as reported in literature **Bulbul et al. (2021)**[77] have reported significantly lower mean absolute neutrophil counts (x10^3/µL) in the preeclamptic women across all three different trimesters. In the first trimester, the values of mean neutrophil counts were significantly lower 6.9±2.6 x10^3/µL in the PE group versus 8.7±3.8 x10^3/µL in the normotensive group; They also noted similar significantly lower neutrophil counts in the second trimester in PE group absolute neutrophil counts 8.2±2.7 x10^3/µL versus 10.2±4.0 x10^3/µL absolute neutrophil counts in the normotensive group; and also in the third trimester with absolute neutrophil counts of 8.5±2.6 x10^3/µL in the PE group versus absolute neutrophil counts of 11.8±3.9 x10^3/µL in the normotensive group. All the mean ANC differences were statistically significant, with **p values <0.001** in each trimester. **Purandare et al. (2022)**[54] also observed a lower mean absolute neutrophil count in the PE group compared to the normotensive group, with values of 8.58±3.64 x10^3/µL and 10.4±3.34 x10^3/µL, respectively, and a statistically significant **p value=0.008**.

- **ABSOLUTE LYMPHOCYTES**: In our study we noted that at recruitment at 16-24 weeks gestation, the mean absolute lymphocyte counts (x10^3/µL) was 1.86±0.47 x10^3/µL in PE group and 1.81±0.46 x10^3/µL in normotensive group, we observed no significant difference in the mean absolute lymphocyte counts between the preeclamptic and normotensive groups, with values of 1.86±0.47 x10^3/µL and 1.81±0.46 x10^3/µL, respectively, p-value=0.650 (refer table 17). Similar to our observation **Mannaerts et al. (2019)**[42] reported mean absolute lymphocyte counts of (1.70±0.62 x10^3/µL) in the PE groups and (1.77±0.49 x10^3/µL) in the normotensive group, and the difference in Means of absolute lymphocyte counts between the two groups was not statistically significant (p=0.533). However, this study is not comparable to ours as this was done in the 3rd trimester compared to our study done in second trimester of pregnancy. **Sabry et al. (2024)**[71] despite noting a higher mean absolute lymphocyte counts (ALC) of (1.8±0.44 x10^3/µL) in normotensive women and (1.3±0.31 x10^3/µL) in preeclamptic women, Found no statistically significant difference in mean ALC in the two groups (p=0.095). However, the mean ALC of (1.8±0.44 x10^3/µL) as reported by them in their normotensive women was similar to our observation of mean ALC of (1.81±0.4 x10^3/µL) in our normotensive women. They noted a lower mean absolute lymphocyte counts of (1.3±0.31 x10^3/µL) in their preeclamptic women compared to our mean ALC of (1.86±0.47 x10^3/µL) in our PE group. The study of **Sabry et al. (2024)**[71] being done in a different trimester (3rd trimester) cannot be compared to our study done in second trimester of pregnancy.

  A study by **Bulbul et al. (2021)**[77] done in a similar second trimester as our study, reported significantly higher mean lymphocytes of (2.2±0.7 x10^3/µL) in PE group, versus (1.8±0.6) in normotensive women and the difference was statistically significant **p<0.001**. **Wang et al. (2019)**[32] also observed similar mean Lymphocytes count of (1.80±0.43) in their normotensive group similar to our observation. However Contrary to our findings, they observed a significantly lower mean Absolute lymphocyte count in their preeclamptic women (1.58±0.47 x10^3/µL) compared to their normotensive women (1.80±0.43 x10^3/µL) and the difference was statistically significant **p<0.01**. Although their results were similar to ours, it is important to note that the studies are not directly comparable due to their being conducted in different trimesters. **Oglak et al. (2021)**[48] observed higher mean absolute lymphocyte counts in both the PE (2.0±0.6 x10^3/µL) and normotensive (2.0±0.5 x10^3/µL) groups compared to the mean values in our study. However, like our study, the difference between the groups was not

statistically significant (p=0.863). But this study is not comparable to ours as this study was conducted in a different trimester (1st trimester compared to our done in second trimester.

- **PLATELET COUNT**: In our study, the mean platelet count was higher in the PE group (228.76±78.93 x10^3/µL) compared to the normotensive group (198.51±74.42 x10^3/µL), but the difference was statistically near to significant (p=0.089) (refer table 17). Contrary to our study, **Bulbul et al. (2021)**[77], observed a statistically significantly higher mean platelet count in the preeclamptic group (237.8±65.7 x10^3/µL) compared to the normotensive group (221.2±60.6 x10^3/µL) with p=0.006. However, they included the platelets of women with severe preeclampsia in their analysis which could have impacted their statistical significance. **Oglak et al. (2021)**[48], observed a statistically significant higher mean platelet counts in the PE group (259.7±48.5 x10^3/µL) compared to the normotensive group (242.5±57.5 x10^3/µL) **p-value=0.015** unlike our observation. Since their study was conducted in a different trimester(1st), a direct comparison cannot be made with our study done in the 2nd trimester of pregnancy. Similar to our observations, **Daud et al. (2022)**[70] in their study despite noting a higher mean platelet count in the PE group (220.00 x10^3/µL) compared to the normotensive group (202.50 x10^3/µL) found no statistically significant difference among the two groups (p=0.90).Though we noted similar finding but our study was conducted in a different trimester (second trimester) compared to their study done in third trimester thus making them uncomparable . **Toptas et al. (2016)**[32] also observed no significant change in the mean platelet counts in Preeclamptic women (217.7±67.3 x10^3/µL) vis a vis normotensive woman (217.19±85.47 x10^3/µL) with p value (p=0.813).

THE TREND OF NLR (NEUTROPHIL-LYMPHOCYTE RATIO) IN PREECLAMPTIC VS NORMOTENSIVE GROUPS (Refer to table 18 & 30)

In our study the mean NLR was slightly higher (3.65±1.06) in PE group vis a vis (3.25 ± 0.95) in normotensive group (3.25 ± 0.95), but the difference was statistically near to significant (p value=0.083) (Refer table 18 & 30). **Sachan et al. (2017)**[69] in study done in second trimester of pregnancy (13-20 weeks) reported mean NLR almost similar to our observation amongst their enrolled subjects. However, they reported a significantly increased mean NLR 3.38±0.16 in PE group compared to 3.14±0.16 in Normotensive group **p-value** <0.01 unlike our

observation. **Panwar et al. (2019)**[31] reported a higher mean NLR amongst subjects enrolled at a similar period of gestation as in our study. However, their Mean NLR was very high 5.55±0.81 in PE group versus 4.55±0.66 in normotensive group and the difference was statistically significant **p-value <0.001** unlike our observation. **Gezer et al. (2016)**[29] reported mean NLR almost similar to our study but this study was done in 1st trimester, they also reported mean NLR in PE group (3.8±1.5) was significantly higher than in normotensive group (3.1±1.3) with p=0.001. In a study done in third trimester **Yavuzcan et al. (2014)**[27] reported a mean NLR of 3.76±1.28 in normotensive group which was similar to our study. But they reported a higher mean NLR of 4.04±2.03 in PE group compared to our observation. However, the difference in means NLR in their two groups was also not statistically significant p value=0.721 which is similar to our observation (refer table: 30). **Yucel et al. (2017)**[25] in their study in third trimester of pregnancy reported statistically insignificant difference in mean NLR of 3.57,3.68 and 3.94 amongst the normotensive, mild PE severe PE groups respectively, p-value =0.707. **Toptas et al. (2016)**[32] in a similar study in 3rd trimester study reported a mean NLR (7.4±5.2) in PE group versus mean NLR (7.2±3.7) in normotensive group and the difference was not statistical significance (p=0.7) However their overall mean NLR in both the groups was much higher compared to our study which may have been due to population and trimester differences. **Mannaerts et al. (2019)**[42] reported a significantly higher NLR in preeclamptic group (6.79±2.84) versus lower NLR in normotensive group (3.60±1.17) (p value= 0.001), the mean NLR in this study was also much higher than that observed in our study and the difference may have been due their sampling having been done in the 3rd trimester after development of hypertension in PE group and normal pregnancies in 3rd trimester in control group. **Singhal et al. (2019)**[65] also reported a statistically significant increased mean NLR in Preeclamptic group 5.64±1.78 compared to Normotensive group mean NLR 4.19±1.00 p<0.001. **Panwar et al. (2019)**[31] also noted a higher mean NLR (5.55±0.81) in PE group versus 4.55±0.66 in normotensive group which was statistically significant P value <0.001) and was much higher than the mean NLR in either group in our study done at a similar trimester of pregnancy. **Serin et al. (2016)**[26], **Gogoi et al. (2019)**[11], **Oylumlu et al. (2014)**[79], reported statistically significant higher mean NLR in the PE group vis a vis the control group (Refer table 30). Hence, the differences in mean NLR in our study compared to others may be attributed to our enrollment and blood sampling of subjects during the second trimester, before the development of preeclampsia in the preeclamptic group. In contrast, most other studies were conducted in the third trimester, after the onset of preeclampsia.

GROUPWISE MEAN NLR IN OUR STUDY IN COMPARISON TO OTHER STUDIES.

(Table: 30)

Authors	Type of Study	Gestational age at blood sampling	N.L.R (MEAN+S.D)		P value
			N	PE	
Our Study	POS	2nd trimester	3.25±0.95	3.65±1.06	0.083
Gezer et al. (2016) [28]	RCC	1st trimester	3.1±1.3	3.8±1.5	**0.001**
Sachan et al. (2017) [29]	PCC	2nd trimester	3.14±0.16	3.38±0.16	**0.01**
Panwar et al. (2019) [31]	PCC	2nd trimester	4.55±066	5.55±0.81	**0.001**
Yavuzcan et al. (2014) [27]	PCC	3rd trimester	3.76±1.28	4.04±2.03	0.721
Yucel et al. (2017) [25]	RCC	3rd trimester	Median (min-max) 3.57(1.70-11.80)	Median (min-max) 3.68(2-14.5)	0.707
Serin et al. (2016) [26]	RCC	3rd trimester	3.9±2.3	5.8±3.1	**0.017**
Toptas et al. (2016) [32]	PCC	3rd trimester	7.2±3.7	7.4±5.2	0.7
Gogoi et al. (2018) [11]	RCC	3rd trimester	3.0±0.98	6.8±7.6	**0.001**
Oylumlu et al. (2014) [30]	PCC	3rd trimester	3.2±1.08	7.39±3.51	**0.001**
Cakmak et al. (2017) [30]	PCC	3rd trimester	3±0.8	5.3±1.4	**0.001**
Singhal et al. (2019) [62]	PCC	3rd trimester	4.19±1.00	5.64±1.78	**0.001**

Abbreviation: Prospective case-control study (PCC); Prospective observation study (POS); Retrospective case-control study (RCC); Preeclampsia (PE); mild preeclampsia (MP); severe preeclampsia (SP); Normotensive (N); Healthy pregnancy (HP); No pregnancy (NP) S.D(Standard deviation); study size (n)

THE TREND OF PLR (PLATELET-LYMPHOCYTE RATIO) IN PREECLAMPTIC VS NORMOTENSIVE GROUPS (refer table 18 & 31)

In our study the mean PLR was significantly higher (125.63±49.55) in PE group vis a vis ± 25.64) in normotensive group (**p value=0.001**) (refer Table 18 & 31). In a first trimester by **Gezer et al. (2016)** [29] noted mean PLR was higher (141.9±50.8) in PE group as compared to mean PLR (118.5±47.2) in Normotensive group and the difference was statistically significant with **p<0.001**. However, mean in PE group and control was higher as compared to the mean PLR of our study this variation may be due to their first trimester sampling. Similar to this 1st trimester study done by **Oglak et al. (2021)**[48] reported a higher mean PLR 137.1±44.9 and 138.1±38.2 in mild and severe PE respectively as compared to mean PLR 121.1±27.4 in control group and the difference was statistically significant **p=0.016**(control vs mild PE) and **p=0.020** (control vs severe PE) However their overall mean PLR in both the groups was higher compared to our study which may have been due to population and trimester differences. **Sabry et al. (2024)** [71] in 3rd trimester study also noted a significantly higher mean PLR in PE group vis a vis normotensive group 113.4±28.1 and 141.2±34.8 respectively with **p<0.001** (refer table: 31).

Gogoi et al. (2019)[11] in 3rd trimester study also reported a higher mean PLR in PE group as compared to normotensive group with a statistically significant difference **p=0.012**.

Singgih et al. (2021)[68] reported a much higher mean PLR in preeclamptic group (161.58±82.64) and normotensive group (160.99±106.43) as compared to the mean PLR observed in our study, although their p-value=0.878 which was not significant and this difference may have been due their sampling having been done in the 3rd trimester after development of hypertension in PE group and normal pregnancies in 3rd trimester in control group. Similar results were noted by **Cintesun et al. (2018)**[61] and **Toptas et al. (2016)**[32] but unlike our study their p-values were not significant (refer table: 31).

Contrary to this **Yucel et al. (2017)**[25] in reported significantly lower PLR in PE group (99.18) versus normotensive women (102.20) with p=0.021. **Bulbul et al. (2021)**[77] in 2nd trimester also reported lower mean PLR in severe PE group (117.4±42.6) versus normotensive group (139.1±66.4) and the difference was statistically significant p=0.009 similar observations were noted in 1st and 3rd trimester in the same study. Similarly, **Jeon et al. (2017)**[55] reported decrease in the mean PLR (119.3±52.8) in PE group as compared to the mean PLR (126.8±36.0) in women with normal pregnancy but the difference was not statistically significant p=0.070.

GROUPWISE MEAN PLR IN OUR STUDY IN COMPARISON TO OTHER STUDIES.

Table: 31

Authors	Gestational age at sampling	PLR (Mean±S.D) & Median		p value
		N	PE	
Our study	2nd trimester	101.12±25.64	125.63±49.55	0.001
Bulbul et al. (2021)[37]	2nd trimester	139.1±66.4	117.4±42.6	0.009
Gezer et al. (2016)[39]	1st trimester	118.5±47.2	141.9±50.8	<0.001
Oglak et al. (2021)[46]	1st trimester	121.1±27.4	137.1±44.9	0.016
Sabry et al. (2024)[31]	3rd trimester	113.4±28.1	141.2±34.8	<0.001
Gogoi et al. (2019)[11]	3rd trimester	9.5±3.6	14.18±14.4	0.012
Cinteza et al. (2018)[40]	3rd trimester	118.05	123.95	0.471
Toptas et al. (2016)[32]	3rd trimester	130.5±86.2	134.4±64.5	0.898
Singgih et al. (2021)[48]	3rd trimester	160.99±106.43	161.58±82.64	0.878
Yucel et al. (2017)[33]	3rd trimester	102.20	99.18	0.021
Jeon et al. (2017)[35]	3rd trimester	126.8±36.0	119.3±52.8	0.070

(PLR: Platelet lymphocyte ratio)

THE TREND OF MPV (MEAN PLATELET VOLUME) IN PREECLAMPTIC VS NORMOTENSIVE GROUPS (refer table 18 & 32).

In our study the mean platelet volume was slightly higher in preeclamptic group (12.01±1.95 fL) than in normotensive group (11.83±2.04 fL) and the difference was statistically non-significant p=0.695(refer table: 18 & 32). **Temur et al. (2021)**[31] in 3rd trimester study reported increased MPV in PE group (9.66±1.62 fL) versus normotensive group (8.92±1.33 fL) and the

difference was statistically significant **p<0.001**. Similar results were observed by **Moraes et al. (2016)**[41] in 3rd trimester study reported that MPV was higher in the PE group (12.1±1.0 fL) than in women with normal pregnancy (10.6±0.9 fL) although their MPV value were similar to our findings, but the difference was statistically significant **p<0.001**. **Kashanian et al. (2013)**[44] & **Mayer-pickel et al. (2021)**[82] in their trimester wise study also noted statistically significant higher MPV in PE group versus Normotensive group (refer table: 32). **Sabry et al. (2024)**[71] noted higher MPV in PE versus Normotensive group 11±2.3 fL and 10±1.3 fL respectively but the difference was statistically non-significant p=0.56. Contrary to this **Cintesun et al. (2018)**[61] noted decreased value of MPV in Preeclamptic group (8.85 fL) as compared to women with normal pregnancy (7.82 fL) and the difference was statistically significant **p<0.001**. The variability in mean platelet volume (MPV) values observed in these studies may be due to the different trimesters in which they were conducted. Like some studies were performed in the third trimester after preeclampsia had already developed.

GROUPWISE MEAN MPV IN OUR STUDY IN COMPARISON TO OTHER STUDIES.

Table: 32

Authors	Gestational age at sampling	MPV (fL) (Mean±S.D) & Median		p value
		N	PE	
Our study	2nd trimester	11.83±2.04	12.01±1.95	0.695
Moraes et al. (2016) [41]	3rd trimester	10.6±0.9	12.1±1.0	<0.001
Temur et al. (2021)[83]	3rd trimester	8.92±1.33	9.66±1.62	<0.001
Cintesun et al. (2018) [61]	3rd trimester	8.85	7.91	<0.001
Sabry et al. (2024)[71]	3rd trimester	10±1.3	11±2.3	0.56
Kashanian et al. (2013) [44]	1st trimester	9.68±1.09	10.2±1.06	0.008
	3rd trimester	9.62±1.12	10.16±1.23	0.009
Mayer-Pickel et al. (2021)[82]	12-14 weeks	10.30	10.55	0.029
	20 weeks	10.45	10.70	0.073
	24 weeks	10.30	10.85	0.011
	28 weeks	10.40	10.90	0.037
	32 weeks	10.50	11.05	0.002
	36 weeks	10.80	11.35	0.015

(MPV: Mean platelet volume)

CORRELATION OF VARIOUS INFLAMMATORY MARKERS WITH EACH OTHER (NLR, PLR AND MPV) [refer table 19]:

Our study identified several key correlations and findings related to hematological parameters in preeclamptic subjects. Specifically, we noted a significant positive correlation between the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), with a **correlation coefficient of 0.323** and a **p-value of 0.000**. We noted a moderate, statistically significant relationship of NLR with PLR i.e. increases in NLR similar increase in PLR was observed.

However, we found no significant correlation between NLR and mean platelet volume (MPV), suggesting that changes in the NLR are not related to changes in MPV. On the other hand, we observed a significant negative correlation between PLR and MPV, with a **correlation coefficient of -0.178** and a **p-value of 0.029**. This suggested that as the PLR increased, the MPV tends to decline [refer table: 19].

In addition to these correlations, we noted an almost significant increase in platelet counts and a significant increase in the platelet-to-lymphocyte ratio among preeclamptic subjects (refer table 17 &18). These increases could be due to a high turnover rate of platelets, leading to their rapid destruction and replenishment. This high turnover is a known characteristic of the hematological changes in preeclampsia. Our findings on platelet trends in PE are in agreement with those reported by **Jaremo et al. (2000)**[40], **Kholief et al. (2019)**[36], **Ahmed et al. (1993)**[58], **Yucel et al. (2017)**[25], **Kurtoglu et al. (2015)**[28], **Moraes et al. (2016)**[41] **and Mannaerts et al. (2019)**[42]. However, despite these similar findings of our study with others on platelet trends in PE, there still remains a lack of clarity about the effect of preeclampsia on platelet diameters, indicating a gap in current research. Further studies are needed to explore this aspect and provide a more comprehensive understanding of the haematological changes associated with preeclampsia.

PREDICTION OF PE USING INFLAMMATORY MARKERS (NLR, PLR & MPV) (refer table 20-22,30-32 & fig 8,9)

- **NLR**: In our study we found a near to significant association of NLR with PE (p value=0.083) using Mann-Whitney U test (refer 18). Using ROC curve analysis with an NLR cut off 3.06, we noted an AUC 0.625(95% CI 0.492-0.759) p value 0.066 with sensitivity of 80.95%, specificity of 51.94%, positive predictive value (PPV) of 21.52% and negative predictive value (NPV) of 94.37% and an accuracy of 56% for early prediction of PE in second trimester of pregnancy. Further on multivariate regression analysis, it was noted that at this NLR cutoff of 3.06, a higher odds of (OR 1.092; 95% CI 0.652-1.830, p=0.738) of developing PE (refer table 21,22 and fig 8) thought it did not reach statistical significance, it was noted that despite the high sensitivity NLR was a weak predictor of PE due to the low specificity, low positive predictive value and low accuracy (56%) (refer table: 33). Using a similar cut off of NLR of 3.08 **Gezer et al. (2016)**[29] noted an AUC of 0.716 with a sensitivity of 74.6%, specificity of 70.1%, PPV of 70.3% and NPV of 74.5% for prediction of PE. Though this study had a similar AUC as our study, they had a lower sensitivity and lower negative predictive unlike our observation, but they had a higher specificity and higher PPV unlike our study. However, they noted a significantly higher odds of developing PE (OR 1.43; 95% CI 1.21-1.76; **p=0.005**) compared to our study. Their study was done in the 1st trimester of pregnancy unlike ours done in second trimester and this difference in timing of the studies could have affected the variable results. Contrary to our observation they reported that NLR was a good predictor of preeclampsia. Another study by **Bulbul et al. (2021)**[27] performed in a similar trimester as ours i.e. 2nd trimester, reported a significant association of NLR with PE **(p-value=0.0001)** unlike our study where we noted the association was near to significance (p-value=0.083). They also reported that NLR at a cut-off value 5.0 and above was a good predictor of PE at with AUC 0.694 on ROC analysis with a sensitivity of 81.37% and a specificity of 55.28%. Though the sensitivity and specificity and AUC were similar to our study but they used a higher cutoff of NLR of 5 compared to our cutoff of 3.06.

  Panwar et al. (2019)[31] reported that NLR cutoff 5.6 had an AUC 0.84 in ROC analysis for prediction of PE with a sensitivity of 73.4% and specificity of 88.6%. Compared to our study they reported a higher specificity for prediction unlike in our study with a lower specificity and the difference may have been due to a higher NLR cutoff used by these authors compared to our cut off of 3.06 (refer table: 33).

Oglak et al. (2021)[46] using NLR cutoff 4.12 NLR reported NLR to be a good predictor of PE with ROC analysis showing AUC 0.76 (95% CI 0.70-0.82) with a high sensitivity of 82.1% similar to our study but a better specificity of 62.0% than our findings. However, this study was done a different trimester i.e. First trimester compared to ours done in a second trimester which could have affected the results. **Sachan et al. (2017)**[69] in their study using NLR cutoff 3.35, which was slightly higher than the cut off used in our study, reported an AUC =0.75 using ROC curve analysis with a sensitivity of 52.9% and a specificity of 74.5% for prediction of PE with a significant diagnostic accuracy of NLR for PE (AUC =0.75, **p=0.01**). As this study was done in first trimester unlike our study, the results are uncomparable. **Kurtoglu et al. (2015)**[28] also found a significant association of NLR with PE. They reported that NLR cutoff 4.48 had the discriminatory ability to differentiate preeclampsia from normotensive women using ROC analysis with AUC 0.596 sensitivity of 57.7%, specificity of 63%, PPV of 73.5%, NPV of 45.5% and accuracy of 59.6%. This study done in the third trimester of pregnancy cannot compared to our study due to different timings of the two studies.

Singhal et al. (2019)[65] suggested NLR was significantly higher in PE group versus normotensive group, and they also noted that NLR cutoff 4.86, had a discriminatory ability to differentiate Preeclamptic and normotensive women. Using ROC curve analysis, they reported an AUC 0.739 with a sensitivity of 68.6%, specificity of 80%, PPV of 77.4%, NPV 71.8% and with an accuracy of 74.3% to differentiate the preeclamptic from normotensive women. This study was done in third trimester of pregnancy and so was uncomparable to our study. **Wang et al. (2019)**[67] also found a significant association of NLR with PE. They reported that NLR had a good diagnostic accuracy to distinguish between PE and normal pregnancy with a slightly lower cutoff 4.198 with AUC 0.70, sensitivity of 53.31%, specificity of 83.22%, PPV of 85.64% and a NPV of 48.73%. This too was done in third trimester of pregnancy and so is uncomparable to our study **Mannaerts et al. (2019)**[42] noted that NLR cutoff 3.92 could discriminate the preeclampsia from normotensive women and using ROC curve analysis they reported an AUC 0.863 (95% CI 0.78-0.94) with a sensitivity of 84.4% and a specificity of 69.4% to differentiate the two groups of normotensive vis a viz preeclamptic women. This study was again done in third trimester and hence not comparable to our study. **Daud et al. (2022)**[70] in a 3rd trimester study noted that NLR cutoff 3.08 using ROC analysis had AUC 0.523 (95% CI 0.43-0.612) with a sensitivity

of 55.3% and specificity of 53.5% to discriminate PE from normotensive group. This study cannot be compared to ours as it was done in a different trimester (3rd) compared to ours done in second trimester (refer table: 33).

TABLE 33: NLR CUT-OFFOF OF OUR STUDY IN COMPARISON TO OTHER STUDIES FOR PREDICTION OF PREECLAMPSIA AND DISCRIMINATION OF PREECLPAMTIC VERSUS NORMOTENSIVE GROUP.

Authors	Inflammatory Marker	Trimester of study	Cutoff Value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
Our Study	NLR	2nd	3.06	0.625 (0.492-0.759) P=0.086	80.95%	51.94%	21.52%	94.37%	58%
Gezer et al. [2016][29]	NLR	1st	3.08	0.716 (0.66-0.76)	74.6%	70.1%	70.3%	74.5%	-
Sachan et al. [2017][30]	NLR	1st	3.35	0.75 P=0.01	52.9%	74.5%	-	-	-
Oglah et al. [2018][28]	NLR	1st	4.12	0.767 (0.70-0.82)	82.1%	62.0%	-	-	-
Bulbul et al. [2021][27]	NLR	2nd	3.0	0.694 (74.5-87.1) p-value=0.0001	81.37%	55.28%	-	-	-
Pinar et al. (2019)[24]	NLR	2nd	3.6	0.84 (0.77-0.90)	73.4%	88.6%	-	-	-
Wang et al. (2019) [17]	NLR	3rd	4.198	0.70 (0.66-0.75)	53.31%	83.22%	85.64%	48.73%	-
Manoranjan et al. [2019][25]	NLR	3rd	3.92	0.863 (078-0.94)	84.4%	69.4%	-	-	-
Singhal et al. [2019][26]	NLR	3rd	4.86	0.739 (0.617-0.861) P=0.001	68.6%	80%	77.4%	71.8%	74.3%
Daud et al. [2018][23]	NLR	3rd	3.08	0.523 (0.433-0.612)	55.3	53.5	-	-	-

[NLR-NEUTROPHIL-LYMPHOCYTE RATIO; PPV-POSITIVE PREDICTIVE VALUE; NPV-NEGATIVE PREDICTIVE VALUE

- **PLR** (refer table 18,20,21,31,34 & fig 8):

  In our study, we observed a significant association of PLR with preeclampsia (**p-value = 0.001**) using the Mann-Whitney U test (refer to Table 18). ROC analysis with a PLR cut-off of 127.80 yielded an AUC of 0.635 (95% CI 0.481-0.790; **p=0.047**), with a sensitivity of 47.6%, specificity of 87.6%, PPV of 38.46%, NPV of 91.13%, and an accuracy of 82% for predicting preeclampsia. Furthermore, multivariate regression analysis indicated that at a PLR cut-off of 127.80 was associated with the significantly

higher odds of developing preeclampsia with an increase by approximately 2.4% (OR 1.024 [95% CI 1.007-1.041], **p-value = 0.005)** (refer to Tables 20, 21 & 22). Our study suggested that PLR can still be a useful predictor of preeclampsia in the second trimester of pregnancy despite its moderate predictive power mainly due to its high specificity, high NPV and the high accuracy combined with a low false positive rate (refer to Tables 20, 21, 31, and Figure 8).

Gezer et al. (2016)[28] noted a that PLR at optimal cut-off 126.8 in the 1st trimester of pregnancy had an AUC 0.705(95% CI 0.656-0.754, **p-value<0.001**), sensitivity of 71.8%, specificity of 72.4%, PPV of 71.1%, NPV of 73.1% for the early prediction of PE. Though they used a similar PLR cut-off as our study, they had a higher sensitivity, positive predictive value for prediction of PE along with a higher odds for developing PE (OR 1.38; 95% CI 1.15-1.63, **p-value=0.008**) than our observations. **Mahmoud et al. (2021)**[83] found a significant association of PLR with PE (**p-value<0.001**). These authors using the PLR cut-off 80.70 in the 1st trimester which was much lower PLR cutoff used in our study (127.80) noted a higher sensitivity of 81.1% and a higher specificity of 95.1% but a lower PPV of 28.6% and NPV of 64.6% but a higher AUC 0.768 (95% CI 0.691-0.846) using ROC curve analysis, for prediction of PE compared to our study. The trimester of sampling may have caused variability in their results as compared to ours as their study was done in 1st trimester of pregnancy.

Oglak et al. (2021)[48] similar to our observation noted a significant association of PLR with PE (**p-value=0.016**). They also reported that PLR at optimal cut-off of 131.8 and above was a good predictor of PE with an AUC 0.631 (95% CI 0.565-0.698, **p-value<0.001**), sensitivity of 65% and specificity of 60.2%. Despite having similar AUC and cut-off as our study they have a lower specificity for the prediction of PE than our observation. Although direct comparison cannot be made between the studies due to the difference in the trimester of sampling.

Kim et al. (2018)[49] also noted that PLR has a significant association with preeclampsia (**p-value=<0.001**). Using PLR cut-off of 116 slightly lower than cut-off used in our study, reported an AUC 0.759(95% CI 0.725-0.791) using ROC curve analysis. They reported that, this PLR cutoff of 116 could be used to differentiate preeclamptic from normotensive women with a sensitivity of 60.1%, specificity of 82.9%, PPV of 73.3% and NPV of 72.7%. They also reported that women PLR with a cutoff of 116 and above had 3.5 times higher odds of developing PE (OR 3.47;95% CI 1.85-6.52, p-

value<0.001). But unlike our study this study was done in 3rd trimester and may have caused variations in their results compared to our study (refer table: 34).

Mannaerts et al. (2019)[42] also noted a significant association of PLR with PE (**p-value=0.0003**). At a lower PLR cutoff of 109 compared to our study using ROC curve analysis, they reported an AUC 0.732 (95% CI 0.616-0.848) and this could differentiate normotensive from preeclamptic women with a sensitivity of 69.7% and specificity of 66% to predict PE. As this study was done in the 3rd trimester it is not comparable to our study. Contrary to our study **Daud et al. (2022)**[79] found no significant association of PLR with PE (p-value=0.75). They reported that PLR at a cut-off value 126.8 in the 3rd trimester of pregnancy similar to the cut-off used in our study reported that women with preeclampsia can be differentiated from normotensive women with a sensitivity of 50.0%, specificity of 51.3% with an AUC 0.486 (95% CI 0.396-0.575, p-value=0.75) which was much lower than that observed in our study. This variation in the result of this study compared to our study noted may be due to trimester difference in the sampling.

Our study demonstrated that PLR, with a cut-off of 127.80 in the 2nd trimester of pregnancy, has moderate predictive power for preeclampsia due to high specificity, high NPV, and high accuracy, despite moderate sensitivity. Comparative studies highlight variations in PLR cut-offs and predictive power, emphasizing the influence of different trimesters and study populations on the results. This underscores the need for further research to standardize PLR use and validate its predictive accuracy across diverse settings.

TABLE 34: PLR CUT-OFFOF IN OUR STUDY IN COMPARISON TO OTHER STUDIES FOR PREDICTION OF PREECLAMPSIA AND DISCRIMINATION OF PREECLPAMTIC VERSUS NORMOTENSIVE GROUP.

[PLR-PLATELET -LYMPHOCYTE RATIO; PPV-POSITIVE PREDICTIVE VALUE; NPV-NEGATIVE PREDICTIVE VALUE]

Authors	Inflammatory Marker	Trimester of study	Cutoff Value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
Our study	PLR	2nd	127.86	0.625 (25.71-70.22) p-value=0.047	47.6%	87.6%	58.46%	91.13%	82%
Gezar et al. (2016)[29]	PLR	1st	126.8	0.705 (0.65-0.75)	71.8%	72.4%	71.1%	73.1%	
Mahmoud et al. (2021)[31]	PLR	1st	80.70	0.768 (0.691-0.846)	81.1%	95.1%	28.6%	64.6%	
Oglah et al. (2021)[30]	PLR	1st	131.8	0.631 (0.565-0.698) p=0.001	65%	60.2%	-	-	-
Kim et al. (2020)[28]	PLR	1st	116	0.759 (0.725-0.791)	60.1%	82.9%	73.33%	72.7%	
Daud et al. (2022)[32]	PLR	1st	126.8	0.486 (0.398-0.575) p-value=0.75	50.0%	51.3%	-	-	-
Manoranjitha et al. (2020)[27]	PLR	1st	109	0.732 (0.616-0.848)	69.7%	66%	-	-	--

- **MPV (MEAN PLATELET VOLUME)** (refer table 21-22,32,35 & fig 8): In our study we found no significant association of MPV with preeclampsia (p=0.695) using Mann-Whitney U test [refer table 18]. Using a MPV cutoff 11.75 fL in 2nd trimester pregnancy for prediction of PE we noted an AUC 0.529 (95% CI 0.400-0.658) with a sensitivity of 61.90%, specificity of 51.94% and PPV of 17.33%, NPV of 89.33% and accuracy of 53.33%. Further on multivariate regression analysis using this MPV cutoff 11.75 fL, we noted the increased odds of developing PE by 15.8% (OR 1.158; 95% CI 0.885-1.515, p=0.286). However, this was a weak and non-significant association of MPV and PE indicates a weak and non-significant association between MPV and preeclampsia Suggesting that MPV is not a reliable predictor of preeclampsia when used in the second trimester [refer table 20,21,22 & fig 8]. The lack of significant association, poor diagnostic performance, suboptimal sensitivity, and specificity, low PPV, and non-significant odds ratio all contribute to this conclusion. **Bulbul et al (2021)**[77] who performed their study in same trimester as ours (2nd) noted a significant association of MPV with PE (**p-value<0.001**) unlike our study. At an MPV cutoff 8.1 fL which is much lower than the cutoff used in our study (11.75 fL) with they noted that prediction of PE could be done with a sensitivity of 81.37 % and specificity of

55.28% with an AUC 0.607 (95% CI 61.8-76.6; **p=0.0006**). Further on multivariate regression analysis they noted that women with MPV cutoff 8.1 fL have a higher odds of developing PE with OR 1.14 (95% CI 1.0178-1.278; **p>0.001**) suggesting MPV can be used for the prediction for PE in 2nd trimester [refer table 33]. **Oglak et al. (2021)**[46] also reported a significant association of MPV with PE (**p-value<0.001**). Using an optimal MPV cutoff 10.65 fL for prediction of PE using ROC analysis with an AUC 0.663 (95% CI 0.598-0.728 **p<0.001**) with a sensitivity of 63.7% and a specificity of 65.0%, indicating MPV is useful for prediction of PE in the 1st trimester of pregnancy. **Mannaerts et al. (2019)**[42] also reported a significant association of MPV with PE (**p-value=0.005**) unlike our study. These authors noted that at MPV cutoff 8.15fL can differentiate preeclamptic women from normotensive women with a sensitivity of 66.7%, specificity of 56.3% and an AUC 0.652 (95% CI 0.515-0.790). Similarly, **Damar et al. (2022)**[45] also found a significant association of MPV with PE (**p=0.02**) unlike our study. Using an optimal cut-off of MPV of 8.95 fL in the 3rd trimester these authors suggested that discrimination between preeclamptic and normotensive pregnancies can be done with a sensitivity of 75.9% and a specificity of 33.3% and with an AUC 0.617 (95% CI 0.523-0.711) (refer table: 35).

While our study did not find MPV to be a significant predictor of preeclampsia in the second trimester, other studies have shown varying degrees of predictive power using different MPV cutoffs and during different trimesters. These discrepancies highlight the need for further research to standardise the use of MPV and validate its predictive accuracy for preeclampsia across diverse populations and settings.

TABLE 35: MPV CUT-OFFOF IN OUR STUDY IN COMPARISON TO OTHER STUDIES FOR PREDICTION OF PREECLAMPSIA AND DISCRIMINATION OF PREECLPAMTIC VERSUS NORMOTENSIVE GROUP.

Authors	Inflammatory Marker	Trimester of study	Cut-off (FL)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
OURS	MPV (fL)	2nd	11.75	0.529 (0.400-0.658) p-value=0.471 NS	61.905%	51.948%	17.333%	89.333%	53.333%
Oglak et al. (2021)[46]	MPV (fL)	1st	10.65	0.663 [0.518-0.728] P<0.000 S	63.7%	65.0%	-	-	-
Balbul et al. (2018)[47]	MPV (fL)	2nd	8.1	0.607 (61.8-76.6) p=0.0006 S	69.57%	54.66%	-	-	-
Mannaerts et al. (2019)[42]	MPV (fL)	2nd	8.15	0.652 [0.515-0.790] p=0.02 S	66.7%%	56.3%	-	-	-
Tamar et al. (2018)[44]	MPV (fL)	3rd	9.15	0.634 (0.587-0.682) p<0.001 S	58.7%	61.7%	-	-	-
Damar et al. (2022)[45]	MPV (fL)	3rd	8.95	0.617 [0.511-0.711] p=0.05	75.9%	33.3%	-	-	-

[MPV-MEAN PLATELET VOLUME; PPV-POSITIVE PREDICTIVE VALUE; NPV-NEGATIVE PREDICITVE VALUE]

ASSOCIATION OF INFLAMMATORY MARKERS WITH SECONDARY OUTCOMES

1. Preterm Deliveries With NLR, PLR & MPV: In our study, 6 (4%) delivered babies were preterm and 144 (96%) were term deliveries (refer table: 23). We found no significant difference in the mean NLR, PLR, and MPV between the preterm and term delivery groups. The preterm delivery group showed slightly higher NLR and PLR values (3.41±0.50 and 110.37±27.76, respectively) compared to the term delivery group (3.30±0.99 and 104.31±31.29, respectively), but these differences were not statistically significant (p>0.05) [refer to Table 24]. Contrary to our findings, **Hrubaru et al. (2022)**[84] reported significantly higher mean NLR (13.75±9.13) and PLR (286.2±195.4) in the preterm delivery group compared to the term delivery group (9.06±7.17 and 237±203.8, respectively) with **p<0.001** and **p=0.007**, respectively. **Akgun et al. (2017)**[85] also observed a significant difference in mean PLR and MPV between the preterm group and the normal weight group (**p<0.001** and **p=0.011**, respectively), with the preterm group showing mean PLR and MPV values of 126.42±64.55 and 8.80±1.70, respectively, compared to 110.90±58.52 and 9.10±1.50 in the normal weight group. Similarly, **Jaffar et al. (2018)**[86] found a significant increase in mean PLR in the preterm group (130.8±81.4) compared to the term delivery group (105.6±55.9) with **p=0.0001**.
2. FETAL BIRTH WEIGHT WITH NLR, PLR & MPV: In our study, we noted out of 150 deliveries 47 (31.3%) were LBW (<2.5kg) and 103 (68.6%) were of normal weight (>2.5kg) (refer table: 23). We found no statistically significant difference in the mean NLR, PLR, and MPV between the low birth weight (LBW) group compared to normal weight group (p>0.05) [refer to Table 25]. **Akgun et al. (2017)**[85], however, observed a significantly higher mean PLR (p<0.001) and MPV (p=0.011) in the LBW group, with mean values of 123.45±60.08 for PLR and 9.40±1.50 fL for MPV, compared to 110.90±58.52 PLR and 9.10±1.50 fL MPV in the normal weight group. In contrast to our findings, **Jaffar et al. (2018)**[86] found a significant negative correlation between PLR and LBW (r=-0.189; **p=0.001**) using the Pearson rank order correlation test. They also reported that a PLR cutoff >80 was associated with a higher risk of adverse neonatal outcomes such as LBW, low APGAR scores, and respiratory distress syndrome (RDS). Similarly, **Tolunay et al. (2020)**[87] unlike our observation reported a statistically significant difference in NLR between the two groups low birth weight and normal birth weight group (**p=0.001**).

3. ASSOCIATION OF MECONIUM STAINED LIQUOR WITH NLR, PLR & MPV: In our study, majority 131 (87.3%) subjects had clear liquor and 19 (12.7%) had MSL (refer table: 23). We noted no association of NLR, PLR and MPV with MSL with p>0.05 (refer table: 27). Similar to our findings **Taskin et al. (2022)**[88] also found no statistically significant association of NLR, PLR, and MPV with MSL.

4. ASSOCIATION OF LOW APGAR ACORE (<7 AT 5 MINUTES) WITH NLR, PLR AND MPV: In our study only 5 (3.3%) neonates had a low APGAR (<7 at 5 min) whereas majority 145 (96%) with normal APGAR score at birth (refer table: 23). We noted no statistically significant association of NLR (p-value=0.208), PLR (p-value=0.961) and MPV (p-value=0.748) with Low APGAR score at birth. The mean NLR, PLR and MPV in low APGAR score group was 2.77±1.05, 103.88±27.86 and 12.14±1.97 fL respectively in those with normal APGAR was 3.33±0.97, 104.58±31.29 and 11.84±2.03 fL respectively and the differences had no statistical significance [refer table 28]. Contrary to our observations **Akram et al. (2023)**[89] reported a positive correlation of PLR with Low APGAR score with **p-value=0.0001** with correlation coefficient 0.69.

5. ASSSOCIATION OF OLIGOHYDRAMNIOS WITH NLR, PLR AND MPV: We found no significant correlation of oligohydramnios with NLR, PLR and MPV. We found one study by **Aram et al. (2023)** were reported a positive correlation of PLR with development of oligohydramnios with corelation coefficient of 0.98 and **p-value<0.001** unlike our observation where we noted no such correlation with oligohydramnios [refer table 26].

6. ASSOCIATION OF NICU ADMISSION WITH NLR, PLR AND MPV: In our study, 8 (5.3%) delivered neonates were shifted to NICU and majority of 142 (95.7%) were shifted to mother side with good condition (refer table: 23). we found no association between NLR, PLR, and MPV with NICU admissions (refer table: 29). However, **Rani et al. (2023)** [90] in a study of 150 neonates, 80 % of neonates who had shifted to NICU for preterm labour and following PROM, had a significantly higher mean NLR, PLR and MPV in women whose neonates with NICU admissions viz a viz women whose neonates did not need NICU care with **p-value>0.05**.

7. ASSOCIATION OF FETAL DEATH WITH NLR, PLR AND MPV: In our study, there were no cases of fetal death (refer table: 23), so we could not establish any association

with NLR, PLR, and MPV. However, **Aslan et al.** (2020)[91] conducted a retrospective study on 150 women with severe preeclampsia and reported a significant association between NLR and fetal loss. They found a notable increase in the mean NLR 6.5 ± 5.4 in the third trimester among women with severe PE who experienced fetal loss, compared to the mean NLR 4.2 ± 2.7 in women with PE without fetal loss (**p = 0.009**). Using an NLR cutoff >3.9 in the prediction of fetal loss among women with severe PE, they reported that, this cutoff had a 75% of sensitivity and 61% of specificity (AUC = 0.684, 95% CI 0.48–0.83, **p = 0.05**).

LIMITATIONS OF STUDY

1. Our study was limited by the inclusion of only low risk women belonging to a labour class population belonging to the lower socioeconomic group excluding other socioeconomic groups.
2. We excluded subjects with obesity, hypertension, diabetes, smokers, which may have affected the results.
3. We did not study the change in haematological parameters across different trimesters with advancing pregnancy.
4. Another limitation is lack of any standardized population specific and trimester specific normograms for inflammatory markers in pregnancy which made comparisons of studies and drawing conclusions difficult but also inappropriate.
5. We suggest larger population based and multicentric cross sectional studies inclusive of all socioeconomic groups excluded in our study, to ensure generalizability of study results.
6. We suggest generation population specific normograms of various haematological parameters trimester wise for normal pregnancies.
7. We suggest larger population based comparative studies on hematological parameters in each trimester before and after development of preeclampsia in all the three trimesters across populations. This will enable us in early identification changes in haematological parameters between normal pregnancies and those with early and late onset PE and mild PE and preeclampsia with severe features.

SUMMARY AND CONCLUSION

Preeclampsia (PE) is a hypertensive disorder condition that occurs during pregnancy. Because of its complicated clinical manifestation involving several organ systems, PE poses substantial risks to both the mother and the fetus, including eclampsia, HELLP syndrome, stillbirth, and different adverse events. Despite ongoing research and the use of serological and inflammatory biomarkers, still no single reliable predictor for preeclampsia has been identified. Early prediction of PE can be enhanced using various expensive biomarkers (PAPP-A, PIGF, sflt-1). Which are not widely available, nor within reach of all, especially in low resource and developing countries. Therefore, exploring inexpensive and cost-effective methods for early PE prediction is crucial to reducing the serious feto-maternal complications of PE by early prediction, diagnosis and timely interventions. Given the role of inflammatory markers in pathogenesis of PE and inconsistencies in existing literature, our study focused on the predictive value of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) during the second trimester (16-24 weeks) for early prediction of PE. The utility of these inflammatory markers in prediction of PE was mainly studied due to its wide availability as they are a part of routine antenatal lab investigations during pregnancy.

AIM: To find the utility of inflammatory markers in second trimester of pregnancy for prediction of preeclampsia.

PRIMARY OBJECTIVES: To find the utility of systemic inflammatory markers NLR, PLR and MPV in second trimester of pregnancy for prediction of preeclampsia.

SECONDARY OBJECTIVES: To find predictive value and association of maternal NLR, PLR and MPV in second trimester with-

1. Severity of Pre-eclampsia.
2. Adverse neonatal outcome like Preterm deliveries, Low birth weight (<2.5kg), Meconium stained liquor, Low APGAR (<7 at 5 min), NICU admission, Neonatal death.

METHOD

This was a prospective observational study conducted on 150 low-risk pregnant women attending Antenatal clinic of ESIC Hospital Noida, after the approval of ethics committee with 2 years study duration and subjects were enrolled in their second trimester (16-24 weeks) in the age group 18 -35 years with a BMI of 18.5- 30 kg /m² after explaining about the study and obtaining their written consent and aforementioned inclusion and exclusion criteria were applied. At enrolment 3ml Blood sample was drawn from study participants for haemogram in EDTA vial and evaluated for NLR, PLR, and MPV. The enrolled subjects were followed during the entire duration of pregnancy until delivery. Note was made of any hypertensive diseases and any other feto-maternal complications which were recorded. Data was entered into an MS Excel spreadsheet and analysed using SPSS version 21.0. Quantitative variables were compared using the unpaired t-test/Mann-Whitney test, and qualitative variables were compared using the Chi-Square test. Diagnostic tests calculated sensitivity, specificity, NPV, and PPV for predicting preeclampsia. Univariate logistic regression determined the odds ratio of NLR, PLR, and MPV as predictors for PE while univariate and multivariate logistic regression analysed their associations with PE. A **p-value** of less than **0.05** was considered significant.

RESULT

Out of 150 participants in our study, 21(14%) developed Pre-eclampsia (PE) in the third trimester of pregnancy, and 129(86%) remained normotensive throughout pregnancy till delivery including the postpartum period. Since our study had only 1 case of severe PE amongst the 21 preeclamptics, this was not included in the separate analysis (Refer Table-14,23 fig-7), We noted following observations in our study.

1. We found no significant association of maternal age, literacy, parity, occupation, diet with preeclampsia.
2. **BMI** majority of subjects in our study were in the normal weight category, 10 % subjects were overweight and 7 % subjects were obese and we found a significant association of BMI with preeclampsia (**p-value=0.001**) and noted the mean BMI was higher in PE group (23.22±2.29 kg/m^2) versus non PE group (20.99±1.56 kg/m^2).
3. The mean absolute neutrophil count (ANC) was, with **p<0.05**, significantly higher in those with preeclampsia (PE) (6.54±1.67x10^3/µL) than in normotensive women (5.53±1.04x10^3/µL).

4. ANC at an optimal cutoff of 7.23x10³/µL in the 2nd trimester of pregnancy in the prediction of PE had an AUC of 0.67 (95% CI 0.52-0.82; **p=0.013**) with 39.13% sensitivity, 99.22% specificity, 90% positive predictive value (PPV), 90.14% negative predictive value (NPV), 0.82% false positive rate, and overall accuracy of 90.13%. Despite its low sensitivity, the high specificity, low false positive rate, and high NPV and overall accuracy make ANC a valuable predictor for ruling out women unlikely to develop PE.

5. There was no significant difference in the mean absolute lymphocyte count (ALC) in the PE versus non PE group, p=0.650.

6. The mean platelet counts were found to be higher in PE group (228.76 x10³/µL) as compared to non PE group (198.51x10³/µL). However, the difference was only near to statistical significance, p=0.089.

7. The mean **NLR** was higher in the PE group (3.65±1.06) compared to the non-PE group (3.25±0.95), and the difference nearing significance (p=0.083).

8. Using NLR at an optimal cutoff of 3.06 on ROC curve analysis showed an AUC of 0.625 (95% CI 0.492-0.759; p=0.066), with a sensitivity of 80.95%, specificity of 51.94%, PPV of 21.52%, NPV of 94.37%, false positive rate of 48.1% and an accuracy of 56%. Using regression analysis, we noted that with increasing NLR the odds of developing PE also increased (OR 1.092; 95% CI 0.652-1.830; p=0.738). It was noted odds ratio (OR) of 1.092 suggests that for each unit increase in the NLR, the odds of developing preeclampsia (PE) increase by 9.2%. However, as the p value was not statistically significant, we cannot confidently state that higher NLR increases the risk of PE.

9. A significant association of PLR with PE was noted with a significantly higher mean PLR in PE group (123.63±49.55) versus non PE group (101.12±25.64) with **p-value=0.001**.

10. Using PLR at an optimal cutoff of 127.80, ROC curve analysis showed an AUC of 0.635 (**p=0.047**) with a sensitivity of 47.62 %, specificity of 87.60 %, False positive rate of 12.4%, PPV of 38.46%, NPV of 91.13%, and an accuracy of 82% for prediction of PE. Using regression analysis, we noted that with increasing PLR the odds of developing PE also increased (OR 1.024; 95% CI 1.007-1.041; **p=0.005**). It was noted that for each unit increase in the PLR, the odds of developing preeclampsia (PE)

increased by 2.4%. Hence PLR can be utilised in the 2nd trimester of pregnancy as a moderate predictor of PE.

11. Mean Platelet Volume (MPV) showed no statistically significant difference in the PE group (12.01±1.95 fL) compared to the non-PE groups (11.83±2.04 fL) with p-value=0.695.

12. We found a significant positive correlation of NLR with PLR with the correlation coefficient of 0.323, **p-value<0.05** and a significant negative correlation of PLR with MPV with correlation coefficient of -0.178, **p-value=0.029**.

13. Out of 21 preeclamptic cases in our study majority 20 subjects were PE with mild features whereas we had only 1 case of severe preeclampsia. Hence, we could not do the comparative sub group analysis of inflammatory analytes with in these groups.

14. Out of 150 deliveries 6 (4%) were preterm and 144 (96%) were term deliveries with the mean NLR, PLR and MPV in the preterm group was (3.30±0.99, 104.31±31.29 and 11.89±2.01 fL compared to 3.41±0.5, 110.37±27.76 and 11.00±2.09 fL in the those who delivered term babies and the difference was not statistically significant with the p-values of 0.797, 0.642 and 0.292 respectively. Hence NLR, PLR and MPV were not useful in the prediction of preterm birth.

15. Out of 150 neonates, 47 (31.3%) were Low birth weight (<2.5kg) and 103 (68.6%) were normal birth weight. The NLR, PLR and MPV in the Low Birth Weight group was 3.43±1.02, 108.00±35.95 and 11.70±1.91 fL compared to 3.25±0.96, 102.98±28.67 and 11.92±2.07 fL in normal birth weight group respectively and the difference was not statistically significant with p values >0.30. Hence NLR, PLR and MPV were not useful in the prediction of low birth weight.

16. Out of 150 subject's, oligohydramnios (AFI <5cm) was noted in 15 subjects (10%) while majority 135 (90%) had normal liquor. We found no statistically significant association of NLR, PLR and MPV with development of oligohydramnios with p-value>0.05.

17. Amongst 150 subjects we noted MSL in 19 (12.7%) subjects and 131 (87.3%) had clear liquor. No significant association of NLR and MPV with MSL was noted in our study p>0.05. However, we found a higher PLR in subjects with MSL with mean PLR of 113.30±42.97 compared to 102.85±28.80 amongst those with normal liquor and the

difference was near to significance p-value=0.07. Hence PLR was a weak predictor of MSL.

18. Out of 150 only 5 (3.3%) neonates had a low APGAR score (<7 at 5 minutes). However, no difference in the mean NLR, PLR and MPV amongst women who had neonates with low APGAR score at birth compared to those with neonates with normal APGAR score. There was no association of low APGAR with inflammatory markers done in the 2nd trimester of pregnancy.
19. Out of 150 subjects who delivered in our study only 8 neonates admitted to NICU of which 5 were for low APGAR, along with MSL, 2 were low birth weight and 1 neonate had RDS. All the neonates had satisfactory outcomes and were discharged in the good condition after NICU stay of a 5 to 10 days.
20. There was no still birth or neonatal death in our study.

CONCLUSION

Our study highlights the importance of the absolute neutrophil count (ANC) and platelet-to-lymphocyte ratio (PLR) as they have been noted as effective and useful tools for predicting preeclampsia (PE) when used during the second trimester of pregnancy. Both markers demonstrate high specificity, negative predictive value (NPV), and accuracy with a low false positive rate in prediction of PE. Although PLR has a low sensitivity of 48% and moderate predictive power in prediction of PE, it can accurately identify at least half the cases of women likely to develop PE with an overall accuracy of 82% and a low false positive rate of 12.4%. We suggest using PLR as a promising screening tool as a "rule out" for low-risk pregnancies unlikely to develop PE and the reason being its high specificity and NPV. This makes it a valuable and cost-effective tool in low-resource settings where expensive biomarkers like PAPP-A, PLGF, and sFlt-1 are unavailable. Our study suggests that pregnant women with a mean PLR value below 127.80 in the second trimester can continue with routine antenatal care, while higher values warrant closer monitoring with selective use of expensive biomarkers (PAPP-A, PLGF, and sFlt-1) and uterine artery Doppler to improve the prediction of PE for early referral to a tertiary care center. This approach optimizes the use of simple tools like the hemogram for identifying inflammatory markers that distinguish between those at risk of developing PE and those not at risk of PE. Implementing such a triaging policy can reduce not only unnecessary referrals to overburdened healthcare facilities in low-resource settings and

help in optimal utilization of expensive biomarkers for improving the early prediction of PE and effective use of available resources especially in lower and middle income countries. This approach will enable the early prediction of PE, allowing for close surveillance and timely intervention of at risk pregnant women which will have the potential to improve not only the immediate feto-maternal outcomes but also long term future health of both the mother and the neonate. We suggest the use of ANC and PLR in early pregnancy as practical, cost-effective tools for managing pregnancy and predicting preeclampsia, particularly in settings with limited resources.

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