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Role of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Predictors of Preeclampsia

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ABSTRACT

Preeclampsia affects 10 million women each year, accounting for 76,000 maternal deaths. Since the one and only effective treatment is delivery of the fetus, it has therefore lead to iatrogenic preterm deliveries and thus causing 500,000 neonatal deaths each year. Preeclampsia also affect s neonatal morbidity to a great extent by causing intrauterine growth restriction, oligohydramnios, iatrogenic low birth weight preterm babies, all of which babies require intensive care. In western countries, incidence is 2-7% out of which 0.1% of them progress to develop seizures, known as eclampsia. To study the efficacy of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in predicting preeclampsia at early second trimester. (13-20 weeks). To study and compare neutrophil to lymphocyte ratio and platelet to lymphocyte ratio measured at 13-20 weeks (before the development of disease) among normotensive, non-severe preeclampsia and severe preeclampsia women. Case control study. 300 Neutrophil and lymphocyte levels are measured using automated cell counter and the corresponding ratios are measured. All enrolled patients are regularly followed up in OPD in their second and third trimesters. Patients who developed preeclampsia are taken as CASES. 5ml venous sample is taken for those who developed disease. Out of 300 women, 68 women developed preeclampsia (52 non severe and 16 severe preeclampsia respectively) and 232 were normotensive. NLR and PLR have shown promising results in many studies on early prediction of preeclampsia. These markers are a part of routine antenatal investigation profile, they are very simple, rapid, non-invasive and easily available predictor tool developed so far in the early prediction of the disease.

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Key Words
Pre eclampsia, NLR, PLR ratio and predictor

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INTRODUCTION

Hypertensive disorder complicating pregnancy is the most common medical disorder in pregnancy. The most deadliest face of this disease is preeclampsia and the resultant eclampsia. Preeclampsia syndrome is a multiorgan disease pertaining to pregnancy, characterized by variable degrees of placental dysfunction and the maternal response to it. PE can affect virtually any organ system thereby contributing to maternal mortality and morbidity. Although it may follow an indolent course in some individuals, it often derails to cause more severe clinical presentations, causing high mortality and morbidity. With sepsis and haemorrhage declining as causes of maternal mortality in the developed world, PE still remains top on this list. Inspite of vast efforts on preventing the complications of the disease, it is still the common cause of maternal mortality and morbidity. Preeclampsia affects 10 million women each year, accounting for 76,000 maternal deaths. Since the one and only effective treatment is delivery of the fetus, it has therefore lead to iatrogenic preterm deliveries and thus causing 500,000 neonatal deaths each year. Preeclampsia also affect s neonatal morbidity to a great extent by causing intrauterine growth restriction, oligohydramnios, iatrogenic low birth weight preterm babies, all of which babies require intensive care. In western countries, incidence is 2-7% out of which 0.1% of them progress to develop seizures, known as eclampsia[1-7].

Objectives:

- To study the efficacy of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in predicting preeclampsia at early second trimester. (13-20 weeks)
- To study and compare neutrophil to lymphocyte ratio and platelet to lymphocyte ratio measured at 13-20 weeks (before the development of disease) among normotensive, non-severe pre-eclamptic and severe pre-eclamptic women.
- To study and compare neutrophil to lymphocyte ratio and platelet to lymphocyte ratio among non-severe and severe pre-eclamptic women before and after the development of disease.

MATERIALS AND METHODS

Aim of the Study To study the role of Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in predicting preeclampsia by early second trimester[7-15].

Study Center: Govt. RSRM Lying in Hospital.

Duration of the Study: October 2019 to September 2020.

Study Design: Case control study.

Methodology:

- All antenatal women of 13-20 weeks gestation attending the antenatal OPD are selected for the study.
- Oral and written consent is obtained after explaining the study.
- Detailed history taken and general, obstetric examination is done.
- 5ml venous blood sample is taken during the enrolment.
- Neutrophil and lymphocyte levels are measured using automated cell counter and the corresponding ratios are measured.
- All enrolled patients are regularly followed up in OPD in their second and third trimesters.
- Patients who developed preeclampsia are taken as CASES.
- 5ml venous sample is taken for those who developed disease.
- Healthy normotensive CONTROLS are those who did not develop preeclampsia during follow up period.
- Statistical comparison was made of the control group and all the patients in respect to NLR and PLR.

Inclusion Criteria: All antenatal women of 13-20 weeks attending the antenatal OPD:

Exclusion Criteria Women with Risk Factors Like:

- Cardiovascular diseases, renal or liver diseases.
- On long term steroids for systemic illnesses.
- Presentational or gestational diabetes mellitus.
- Patients with history of membrane rupture.
- Patients with history of any infection.
- Patients with Multiple pregnancies.

Sample Size: 300.

Data Collection: Detailed proforma enclosed along with.

Analysis Plan: Statistical analysis.

Sponsorship: None.

Conflict of Interest: None.

RESULTS AND DISCUSSIONS

Table 1: Percentage of Preeclampsia

Sample size	300
Normotensive	232 (77%)
Non severe preeclampsia	52 (17%)
Severe preeclampsia	16 (6%)

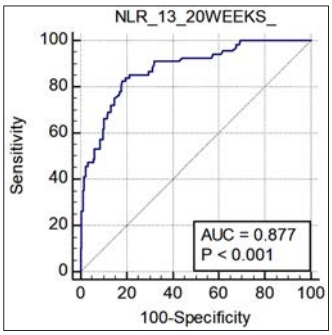

Chart 1: ROC Curve for NLR at 13-20 Weeks

Table 2: Area Under the ROC Curve (AUC)

Area under the ROC curve (AUC)	0.877
Standard Error a	0.0239
95% Confidence interval b	0.834- 0.912
z statistic	15.753
Significance level P (Area=0.5)	**<0.0001**
Youden index J	0.6443
Associated criterion	**>4.65**
Sensitivity	**83.82**
Specificity	**80.60**

- Using ROC curve analysis, NLR was found to have 83.82% sensitivity and 80.6% specificity at a cut off value of 4.65 in predicting preeclampsia at 13-20 weeks gestation.

Table 3: NLR T Test

		N	Mean	Std. Deviation	Std. Error Mean	P-value
NLR (13-20 Weeks)	Normotensive women	232	**3.4533**	1.28672	.08448	0.000
	Pre-eclamptic women	68	**5.9928**	1.77527	.21528	

- The mean NLR of normotensive women at 13-20 weeks was 3.453 and that of women who developed preeclampsia was 5.992.
- P value here is 0.00 (<0.05) so there exists a statistical signifance of NLR measured at 13-20 weeks between normotensive women and women who developed preeclampsia.

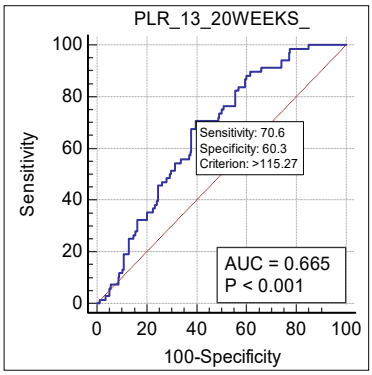

Chart 2: ROC Curve of PLR at 13-20 Weeks

Table 4: Area Under the ROC Curve (AUC)

Area under the ROC curve (AUC)	0.665
Standard Errora	0.0338
95% Confidence intervalb	0.608-0.718
z statistic	4.864
Significance level P (Area=0.5)	**<0.0001**
Youden index J	0.3093
Associated criterion	**>115.27**
Sensitivity	**70.59**
Specificity	**60.34**

- Using ROC curve analysis, PLR was found to have 70.59% sensitivity and 60.34% specificity at a cut off value of 115.27 in predicting preeclampsia by 13-20 weeks gestation.

Table 5: PLR T Test

		N	Mean	Std. Deviation	Std. Error Mean	P-value
PLR (13-20 Weeks)	Pre-eclamptic Women	68	137.28618	38.534746	4.673024	0.001
	Normoten-sive Women	232	115.10594	49.507653	3.250337	

This prospective case control study was conducted in Govt. RSRM lying in hospital during the period of October 2019 to September 2020 to find out the potential of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in predicting preeclampsia early and thus to provide the women with better antenatal care and therapeutics in view of decreasing the disease severity. 300 women attending the antenatal clinic were studied. NLR and PLR values were calculated from the complete blood count taken at 13-20 weeks gestation. They were followed up till postpartum 6 weeks. Women who developed preeclampsia were taken an another complete blood count for finding out the NLR and PLR after development of disease. Out of 300 women, 232 women normotensive and 68 women developed preeclampsia. 52 and 16 women developed non severe and severe pre-clampsia respectively. The mean age of normotensive women was 23 and that of preeclamptic women was 24 and there was no statistical significance between age and preeclampsia. 38.5% of teenage women developed preeclampsia and thus an increased incidence of preeclampsia among teens was observed when compared with the other age groups. Also no statistical significance was made out between the occurrence of preeclampsia with respect to obstetric score and BMI. The mean BMI of women who developed preeclampsia was 25.7 and the mean BMI of normotensive women was 26.05. The mean NLR of non-severe pre-eclamptic women before development of disease was found to be 5.42 and that of the severe pre-eclamptic women was 7.83.Thus NLR proved to be a good discriminator of severe and non-severe pre-clampsia. The mean NLR of non-severe

pre-eclamptic women after the development of disease was found to be 6.53 and that of the severe pre-eclamptic women was 10.29. Thus NLR discriminates the disease severity after the development of the disease. Mean NLR of pre-eclamptic women before and after the development of disease was found to be 5.99 and 7.41 respectively. In Prasmusinto *et al.* study, the mean NLR after development of disease was 14.91.In Kortugulu *et al.* study in 2014, the mean NLR was 14.48. And in many other studies done by Gezer *et al.,* Olylum *et al.* etc. the NLR was elevated statistically significant than their normal counterparts. Mean PLR of pre-eclamptic women before and after the development of disease was found to be 137.28 and 170.27 respectively. Mean PLR of non-severe pre-eclamptic and severe pre-eclamptic women before the development of disease was 134.45 and 146.5 respectively. Thus in my study women who developed preeclampsia had higher neutrophil to lymphocyte ratio and platelet to lymphocyte ratio both before and after development of the disease when compared with their healthy controls. Many studies compared the mean NLR in healthy and preeclamptic women. Receiver Operating Curve analysis was plotted for both NLR and PLR in finding out their predictive accuracy for preeclampsia. In my study, NLR had a sensitivity of 83.82% and specificity of 80.6% at a cut off value of 4.65 and PLR had a sensitivity of 70.59% and specificity of 60.34% at a cut off value of Study done by C. Gezer *et al.* found a 74.6% sensitivity and 70.1% specificity of NLR in predicting preeclampsia at a cut off value of 3.08. In Mannaerts *et al.*, NLR was found to have sensitivity of 84.4% and specificity of 69.7% at a cut off value of 3.92. PLR was found to have sensitivity of 69.7% and specificity of 66% at a cut off value of 109. Yavuzcan et al. in his study found that NLR values were significantly higher in women who had severe preeclampsia than their healthy counterparts. Kurtoglu *et al.* in his retrospective study found that there was a significant raise in NLR in pre-eclamptic women. Studies have also been made to study the exaggerated platelet activity that is seen in preeclampsia. The endothelial dysfunction which activates the thrombocytes in the maternal circulation is the rationale behind these studies. They studied the PDW platelet distribution width, MPV mean platelet volume and PCT plateletcrit which are better indicators of the activated thrombocytes and thus the endothelial dysfunction that is going on in the background. Thereby these studies help us in predicting the disease before the onset of signs and symptoms. Aysekirbas *et al.* study on the platelet indices showed that platelet distribution width PDW was higher in patients who were destined to develop preeclampsia[15-20].

Comparison of NLR with Previous Studies

Year of the Study	Study done By	Sample Size	NLR Cut off Value	Sensitivity	Specificity
2016	C. Gezer	430	3.08	74.6%	70.1%
2014	Oylumlu	306	4.1	83.3%	81.5%
2017	Mannaerts	164	3.92	84.4%	69.4%
2020	Our Study	300	4.67	83.82%	80.6%

Summary: This study was done at Govt. RSRM lying in hospital to study the efficacy of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in predicting preeclampsia early at their early second trimester. Thus these indicators can be in helpful in early prediction and thus help us in early interventions and strict surveillance to reduce the disease severity.

- Out of 300 women, 68 women developed preeclampsia (52 non severe and 16 severe preeclampsia respectively) and 232 were normotensive.
- Out of 68 women, 14 women developed preeclampsia before 34 weeks and 54 women after 34 weeks.
- The mean age of pre-eclamptic women was 23 and that of normotensive women was 24.
- 38.5% of women from age group 20 and below developed preeclampsia.

This shows the increased incidence of preeclampsia in teens. Out of 16 severely pre-eclamptic women, 13 of them were from the age group of 25 and below.

- 15.4% of women from age group 20 and below developed severe preeclampsia (which is more among all the age groups). This shows how common is severe preeclampsia in teenage and elderly women.
- The independent samples test was drawn between age and preeclampsia to find the p value which was 0.096 (>0.05), so there doesn't exist a correlation between age and preeclampsia.
- 25.4% of primigravida (5.3% severe and 20.1% non-severe), 24.2% of second gravida, 6.2% of third gravida developed preeclampsia. So high incidence of preeclampsia among primigravida has been observed.
- The mean BMI of women who developed preeclampsia was 25.7 and the mean BMI of normotensive women was 26.05.P value drawn between BMI and preeclampsia was 0.542 (>0.05), so there doesn't exist a statistical significance between BMI and preeclampsia. There was also no

statistical significance found between abortion history and preeclampsia.

- 41.1% of pre-eclamptic women had LSCS whereas only 28.8% of normotensive women had LSCS. Increase in caesarean section rate was noted in pre-eclamptic women. The indications were IUGR with Doppler changes, severe oligohydramnios, fetal distress, unfavourable cervix, uncontrolled BP and previous caesarean section.
- Only 9.6% of normotensive women had preterm babies whereas almost 30% of pre-eclamptic women had preterm deliveries due to the iatrogenic prematurity caused by pregnancy termination done at earlier gestational age for maternal benefits.
- Using ROC curve analysis, NLR was found to have 83.82% sensitivity and 80.6% specificity at a cut off value of 4.65 in predicting preeclampsia by 13 to 20 weeks gestation.
- PLR was found to have 70.59% sensitivity and 60.34% specificity at a cut off value of 115.27 in predicting preeclampsia by 13 to 20 weeks gestation.
- The mean NLR of pre-eclamptic women at their early 2nd trimester at 13-20 weeks gestation (before the development of the disease) and after the development of disease was found to be 5.99 and 7.41 respectively.
- The mean NLR of normotensive women at 13-20 weeks was 3.45.
- The mean NLR of non-severe pre-eclamptic women before development of disease was found to be 5.42 and that of the severe pre-eclamptic women was 7.83.
- The mean NLR of non-severe pre-eclamptic women after the development of disease was found to be 6.53 and that of the severe pre-eclamptic women was 10.29.
- The mean PLR of pre-eclamptic women at their early 2nd trimester at 13-20 weeks gestation (before the development of the disease) and after the development of disease was found to be 137.28 and 170.27 respectively.
- The mean PLR of normotensive women at 13-20 weeks was 115.1.
- The mean PLR of non-severe pre-eclamptic women before development of disease was found to be 134.4 and that of the severe pre-eclamptic women was 146.5.

CONCLUSION

There are many studies involving bioassays like PAPP-A and beta hCG and many other biochemical and inflammatory markers in finding an efficacious, non-expensive, simple, non-invasive predictor for preeclampsia. Inspite of several significant advances in knowing the etiopathogenesis of preeclampsia, we are still unable to find a reliable predictor for preeclampsia which satisfies all the above criteria. NLR and PLR have shown promising results in many studies on early prediction of preeclampsia. These markers are a part of routine antenatal investigation profile, they are very simple, rapid, non-invasive and easily available predictor tool developed so far in the early prediction of the disease.

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