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Can High First Trimester NLR And PLR is Early Predictor for Preeclampsia?: An Experience of Single Tertiary Care Center

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Abstract

***Objective:** Aim of present study was to determine whether first-trimester neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) would be useful indicators of subsequent preeclampsia.*

***Material and Methods:** Medical records of 146 women (age range 20-36 years; mean age 27.27 years) with preeclampsia and healthy controls were retrospectively evaluated at our hospital. Both groups were evaluated in terms of clinical characteristics and first-trimester haematological parameters including hemoglobin, neutrophil, lymphocyte, platelet, NLR and PLR. Receiver operating characteristic curve (ROC) analysis was also performed to identify the optimal NLR and PLR levels predicting preeclampsia.*

***Results:** Of the 146 patients, 70 (~47.9%) were preeclamptic patients and remaining 76 (52.1%) were normotensive in present study. In the haematological parameters, lymphocyte ($p < 0.001$), NLR ($p < 0.0001$) and PLR ($p < 0.0001$) levels were significantly elevated in the preeclampsia women. Whereas other parameters neutrophil ($p\sim0.07$), platelet ($p\sim0.124$) hemoglobin concentration ($p\sim0.436$) were not significantly high or low in the preeclamptic women. On multivariate regression analysis, NLR (OR 2.17; 95% CI 1.04-4.51; $p = 0.03$) and PLR (OR 1.02; 95% CI 1.01-1.04; $p = 0.01$) were the independent powerful predictive variables. In the ROC analysis, for both NLR and PLR area under curve was 0.800. The cut-off values of NLR >2.78 and PLR >109 predicted preeclampsia with the sensitivity of 80.0% and 85.7% and specificity of 71.1% and 65.8%, respectively.*

***Conclusions:** We concluded that high NLR and PLR in the first trimester is the strong predictor of subsequent preeclampsia.*

Keywords: neutrophil to lymphocyte ratio (NLR); platelet to lymphocyte ratio (PLR); preeclampsia

Introduction

Preeclampsia is a multisystem disorder characterized by a new onset hypertension and proteinuria after 20 weeks of gestation in a previously normotensive pregnant woman.[1] It is one of the most common complications of pregnancy, affecting 5-10% of all pregnant women and is responsible for 12% of the global maternal mortality.[2,3]

Its etiology and pathophysiology remain enigmatic. The Common proposed pathophysiologyis altered immune response of gravid woman causes excessive maternal inflammation and abnormal placentation. These lead to multisystemic endothelial dysfunction in form of increased capillary permeability, Micro-vascular thrombosis and Increased vascular tone.[4]

Rationale behind the early detection of the preeclampsia isearly detection would allow for timely initiation of the preventive therapy to reduce the risk of preeclampsia associated mortality and morbidity.[5-8] Proposed biomarkers for early detection of preeclampsia are summarized in table 1.[9-11] These biomarkers and uterine artery pulsatility index for early diagnosis of preeclampsia has no widespread acceptancein clinical practice.[12,13]

Table 1. *Proposed biomarkers for early detection of preeclampsia*[9]

Category	Name of biomarker
Angiogenic marker	VEGF, sflt-1,PIGF, sEng
Renin angiotensin system related	Antibodies against the AT1 receptor
Immunological markers	PP-13, PAPP-A , ADAM12
Metabolic marker	Visfatin
Endocrinological markers (Maintenance of spiral artery function)	Activin A, Inhibin A

VEGF-vascular endothelial growth factor; sFlt-1-soluble fms-like tyrosine kinase-1; PIGFplacental growth factor;; sEng - soluble endoglin; AT1 receptor -Angiotensin II receptor type 1; ADAM12- metalloprotease 12; PP-13- placenta protein 13; PAPP-A-pregnancy-associated plasma protein A

Recently, systemic inflammatory response markerssuch like neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have significant interest in various clinical circumstances. Elevated levels of systemic inflammatory response markers are significantly associated with increased cardiovascular risk and mortality in some malignancies.[14] However, the use ofsystemic inflammatory response markers in the early prediction of preeclampsia remains unclear.

So aim of present study was to assess the predictive value of systemic inflammatory response markers neutrophil-to-lymphocyte ratio (NLR), Platelet-to-lymphocyte ratio (PLR) in the early prediction of preeclampsia.

Materialand Methods

This is a retroaspective observational study,perfomed in the department of Obstetrics and Gynaecology, SantokbaDurlabhji Memorial Hospital cum Medical Research Institute, Jaipur, Rajasthan, India between June 2017 to March 2018. Medical records of 146 women (age range 20-36 years; mean age 27.27 years) with preeclampsia and healthy controls were retrospectively evaluated at our hospital. Inclusion and exclusion criteria for both group are

Inclusion Criteria

- **Test group-** 70 Preeclamptic women diagnosed as per American College of Obstetricians and Gynecologists (ACOG) criteria. All preeclamptic patients were diagnosed between 24 to 40 weeks of gestation.
- **Control group-** 76 pregnant women delivered between 37 to 41 weeks, appropriate for gestational age, without any history of complications throughout the pregnancy

Exclusion criteria

- Patients with systemic diseases,
- History of hematopoietic system disorders,
- Malignancies,
- Acute or chronic inflammatory disease

Complete blood count(CBC) was performed in the first trimester (between 7 to 13 weeks of gestation) at our centre using automated machine. Both groups were evaluated in terms of clinical characteristics and first-trimester hematological parameters including hemoglobin, neutrophil, lymphocyte, platelet, NLR and PLR. Approval of the institutional ethical committee was obtained for this retrospective study.

Receiver operating characteristic curve (ROC) analysis was also performed to identify the optimal NLR and PLR levels predicting preeclampsia.Data analyses were performed with SPSS version 11.0 (Chicago, Illinois). $P<0.05$ considered as the significant level

Results

Of the 146 patients, 70 (~47.9%) were preeclamptic patients and remaining 76 (52.1%) were normotensive in present study. Clinical characteristics of the recruited patients are shown in tabular form in table number 2. In the haematological parameters, lymphocyte ($p < 0.001$), NLR ($p < 0.0001$) and PLR ($p < 0.0001$) levels were significantly elevated in the preeclampsia women. Whereas other parameters neutrophil ($p\sim0.07$), platelet ($p\sim0.124$) hemoglobin concentration ($p\sim0.436$) were not significantly high or low in the preeclamptic women.

Table 2. *Clinical characteristics of the recruited patients*

Parameters	Pre eclampsia group (n=70) (Mean ± SD)	Normotensive group (n=76) (mean ± SD)	P value
Maternal age (in years)	27.5±3.6	27.1±3.5	0.579
Hemoglobin	11.4±1.4	11.7±1.1	0.43
Birth weight (in kg)	2.7±0.5	3.9±0.4	0.02
Gestational age at delivery (In weeks)	39.5±2.2	40.7±2.3	0.03
Neutrophyl ($10^{3}/mm^{-3}$)	6.9±1.4	6.2±1.8	0.07
Lymphocyte ($10^{3}/mm^{-3}$)	2.5±1.6	2.0±0.5	<0.001
Platelet ($10^{3}/mm^{-3}$)	280.4±80.4	253.8±65.6	0.125
NLR	3.53±0.9	2.6±0.9	<0.001
PLR	151.2±48.0	106.1±33.7	<0.001

NLR- neutrophil-to-lymphocyte ratio; PLR Platelet-to-lymphocyte ratio

On multivariate regression analysis, NLR (OR 2.17; 95% CI 1.04-4.51; p = 0.03) and PLR (OR 1.02; 95% CI 1.01-1.04; p = 0.01) were the independent powerful predictive variables as shown in table number 3.

Table 3. *Significant predictors of preeclampsia in multivariate regression analysis*

Markers	Odd ratio	95% CI	P value
NLR	2.2	1.04-4.51	0.03
PLR	1.02	1.01-1.04	0.01
Lymphocyte	1.1	0.95-1.87	0.105

CI- confidenseintervel; NLR- neutrophil-to-lymphocyte ratio; PLR Platelet-to-lymphocyte ratio

In the ROC analysis(Figure 1), for both NLR and PLR area under curve was 0.800. The cut-off values of NLR>2.78 and PLR >109 predicted preeclampsia with the sensitivity of 80.0% and 85.7% and specificity of 71.1% and 65.8%, respectively as shown in tabular form in table number 4.

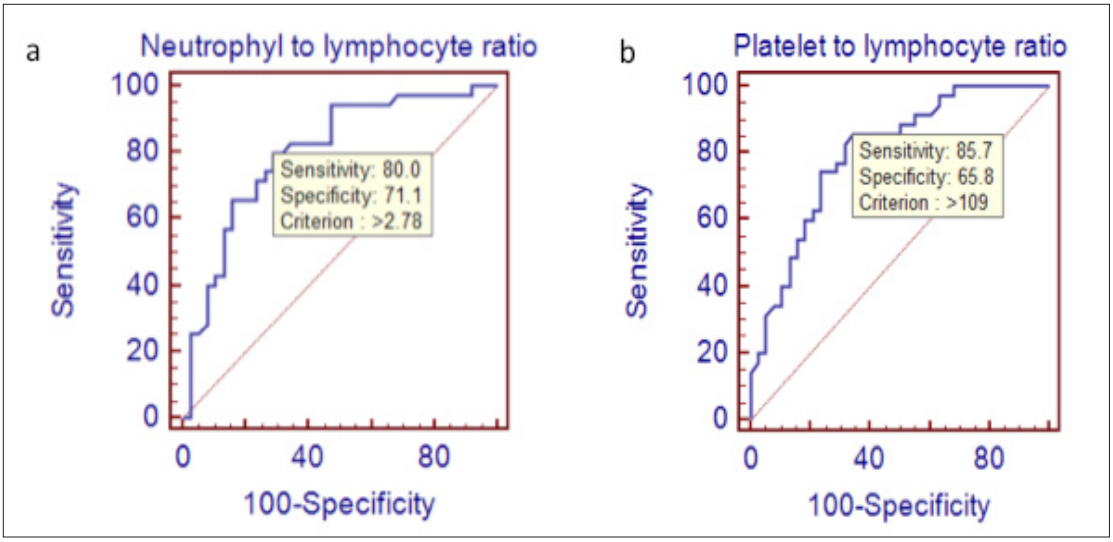

Figure 1. *Receiver operating characteristic (ROC) curves for (a) neutrophil-to-lymphocyte ratio (NLR) and (b) Platelet-to-lymphocyte ratio (PLR) to predict the early diagnosis of preeclampsia. The area under the ROC curves for both parameters was 0.800.*

Table 4. *Cut- offs value for first trimester NLR and PLR in predicting eclampsia*

Markers	AUC (95% CI)	Sensitivity	Specificity	Cut-off value	P value
NLR	0.800 (0.690 to 0.885)	80.0%	71.1%	>2.78	0.0001
PLR	0.800 (0.690 to 0.885)	85.7%	65.8%	>109	0.0001

AUC- Area under the curve; NLR- neutrophil-to-lymphocyte ratio; PLR Platelet-to-lymphocyte ratio

Discussion

Preeclampsia is a result of abnormal placentation which is the sequelaeof altered immune response and excessive maternal inflammation. Systemic inflammatory response markers such as NLR and PLR , implying the presence of an increased inflammatory state. So they can predict preeclampsia in the first trimester of pregnancy.Present study was planned to assess the systemic inflammatory markers NLR and PLR in the first trimester in the patients with preeclampsia.

To assess the NLR and PLR parameters in the early prediction of the preeclamsia, Gezer at al[15,] Oylumlu et al [16] and **Kurtoglu**et al[17] reported that NLR was significantly higher in preeclamptic patients as compare to the control group of patients. While Mannaertset al.[18] found that NLR was higher and PLR was lower in the PE group compared to the controls and Kurt et .al.[19] found that NLR was not significantly different between PE and control groups of patients, although the neutrophil count was significantly higher in the group with PE patients. In present study lymphocyte, NLR and PLR levels were significantly elevated in the preeclampsia women whereas other parameters neutrophil (p~0.07), platelet (p~0.124) hemoglobin concentration (p~0.436) were not significantly high or low in the preeclamptic women.

On multivariate regression analysisGezer at al[16] found that NLR (OR 1.43) and PLR (OR 1.38) were the most powerful predictive variables near similar to the present study NLR (OR 2.17) and PLR (OR 1.02). Gezer at al [7] found that areas under the ROC curve were 0.716 and 0.705 for NLR and PLR, respectively. The cut-off values of NLR ≥ 3.08 and PLR ≥ 126.8 predicted preeclampsia. In present study the ROC analysis, for both NLR and PLR area under curve was 0.800. The cut-off values of NLR >2.78 and PLR >109 predicted preeclampsia.

Limitations of Present Study

- Present study was conducted in the limited geographical area and on relatively small sized sample. To extrapolate our results in the whole population, this study should be conducted in the large geographical area and on big sized sample
- This is a retrospective study so unidentified confounding factors has been introduces.
- Present study was not correlated with the other radiological and biochemical for preeclampsia

Summary

Among all proposed first trimester biomarkers and sonological markers, CBC is the universally prescribed haematological test, only we have to see the NLR and PLR carefully. Which would be cost effective and might be most beneficial not only for pregnant women but also for whole of the society. As high NLR and PLR has been associated with increased inflammation, so if it has been done in acute inflammatory condition it should not be interpreted. Pregnant women suffering from chronic inflammatory condition or some hematopoietic systemic disorder may show elevated NLR and PLR.

Conclusions

We concluded that high NLR and PLR in the first trimester is the strong predictor of subsequent preeclampsia. Thus, we suggested that pregnant women with high NLR and PLR during the first trimester of pregnancy should be monitored closely for signs of preeclampsia such as hypertension and proteinuria.

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