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Diagnosis of Preeclampsia using Neutrophil Lymphocyte Ratio and Platelet Lymphocyte ratio:A retrospective case control study from a teaching Hospital in Rural Maharashtra.

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ABSTRACT

Aim: Pregnancy is a state of low grade inflammation.NLR and PLR are said to be low cost,easily available markers of inflammation.

The aim of our study is to evaluate the diagnostic accuracy of NLR and PLR in prediction of preeclampsia and its severity.

Methods: We conducted a retrospective case control study on 67 preeclamptic women and 70 women with healthy pregnancy.The patients were divided into 3 groups of controls.mild and severe preeclampsia.The CBC at the time of admission for labour was noted and the blood cell indices were calculated and compared between 3 groups .

Results : There was no significant difference in the values of NLR,PLR , RDW,absolute neutrophil and lymphocyte count and platelet count between normal and preeclamptic patients.

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Conclusion: Prospective cohort studies on a larger scale are needed before we can start using NLR ,PLR and RDW routinely in clinicl setting to diagnose preeclampsia and to assess its severity.
Keywords: NLR,PLR,Preeclampsia

Pre-eclampsia is a multisystem disorder characterized by new-onset hypertension and proteinuria after 20 weeks of gestation(1)
It is a leading cause of maternal morbidity worldwide(2). Ten percent of women have high blood pressure during pregnancy, and preeclampsia complicates 2% to 8% of pregnancies all over the world(3)
Hypertensive disorders are major contributors to maternal deaths in developing countries,accounting for nearly 18% of maternal deaths world wide(4)
Improving the outcome for preeclampsia necessitates early prediction of the disease to identify women at high risk.Effective intervention such as Aspirin prophylaxis can be used in women who have been identified in early pregnancy(5). Low-dose aspirin given to high risk pregnant women in the first trimester of pregnancy has been said to lower the risk of preeclampsia upto 24%.(6)
It has been reported that women with Preeclampsia have chronic inflammation . There is placental ischemia in preeclampsia due to trophoblast invasion .This leads to an immune imbalance which causes chronic inflammation . This immune imbalance also leads to the development of vascular endothelial dysfunction and hypertension (7)
Recent studies have shown that measuring ratio of blood cell subtypes such as the neutrophil lymphocyte ratio (NLR) ,platelet lymphocyte ratio (PLR) and RDW (red cell distribution width) may provide clue to diagnosis of diseases with underlying low-grade inflammation such as preeclampsia.
A metaanalysis on the predictive role of preeclampsia by Kang et al has found that NLR value is higher in preeclampsia patients especially in severe preeclampsia and have postulated that NLR may be used as a laboratory marker for prediction and evaluation of preeclampsia(8)

NLR and PLR are simple and inexpensive markers of inflammation which can be easily calculated from the complete blood count .This makes these markers a cost-effective tool to assess preeclampsia in a clinical setting.

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Aims : Aim of our study is to evaluate the diagnostic accuracy of NLR and PLR in prediction of preeclampsia.

Methods

This is a retrospective record based case-control study that was conducted in the Department of Obstetrics and Gynecology at a teaching hospital in rural Maharashtra from January 2019 to December 2019.

Ethical clearance was taken from the Ethical committee of SMBT Institute of Medical Sciences and Research Centre,Nashik,India.

The study group consisted of patients diagnosed with preeclampsia who were admitted to our hospital for delivery.The control group consisted of healthy pregnant women without any pregnancy complications who delivered within the same time .

Pregnant women who had a history of diabetes ,heart disease, chronic renal disease and those diagnosed with clinically diagnosed infectious diseases were excluded from the study.

Pregnant women having ruptured membranes and multiple pregnancies were also excluded from the study.

Demographic data including age, parity,gestational age ,mode of delivery and birthweight were recorded .

Gestational age was determined based on the first day of the last menstrual period (LMP) as noted in the case records.It was confirmed with first trimester ultrasonographic measurement of the crown–rump length (CRL).

Diagnostic criterion of Preeclampsia was based on 2013 guidelines of ACOG(9)

Mild Preeclampsia was defined as the presence of hypertension (blood pressure >140/90 mmHg) associated with proteinuria in women known to be previously normotensive.

The diagnosis of severe preeclampsia was based on the presence of systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mmHg and proteinuria.

The patients were classified into 3 groups with normal BP(group 1) or mild preeclampsia (group 2) and severe preeclampsia (group 3).

The CBC at the time of admission for labour was noted .

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The primary outcome of interest were the Neutrophil Lymphocyte ratio and the Platelet Lymphocyte Ratio.A few secondary outcomes like the Red cell distribution width,absolute neutrophil count,absolute lymphocyte count and Haemoglobin were also compared.

NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count.

PLR was defined as the absolute platelet count divided by the absolute lymphocyte count.

The NLR and PLR were retrospectively analyzed and compared between normal patients,patients with mild preeclampsia and severe preeclampsia.

Data was entered in Excel spreadsheet and data analysis was done using Excel software.Mean and standard deviation was calculated for continuous variables and percentages were calculated for categorical variable.The data was compared using Student T test.p value less than .05 was considered significant.

Results

Table 1: Comparison of Demographic and clinical characteristics between study and control group.

Name of the Variable	Control(a)	Preeclampsia		P(a+b)	P(b+c)	P(a+c)
		Mild(b)	Severe ©			
Maternal age (years)	23.94±3.69	23.29±3.82	23.14±2.96	0.383	0.881	0.386
Gestational age at delivery (weeks)	38.17±3.23	36.84±4.03	36.50±4.51	0.251	0.884	0.372
Neonatal birth weight (g)	2.57±0.50	2.25±0.70	1.80±0.37	0.016	0.004	0.000
Systolic BP (mmHg)	112.83±9.56	144.73±6.95	171.29±9.53	0.000	0.000	0.000
Diastolic BP (mmHg)	71.74±7.79	94.20±6.24	115.71±6.46	0.000	0.000	0.000

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A total of 137 patients were enrolled in the study. 67 patients with preeclampsia who delivered during the study period who met the inclusion criterion were included in the study.70 normal ,healthy pregnant women who delivered during the same period were taken as controls.There were 53 patients with mild preeclampsia and 14 patients with severe preeclampsia in the study group.

The mean maternal age in our study was 23 years and there was no statistical difference between the 3 groups of patients with normal BP,mild preeclampsia and severe preeclampsia.

The patients with preeclampsia delivered on an average earlier than the patients with normal blood pressure(38 weeks vs 36 wks) but this difference was not statistically significant.

The highest birth weight was found in the control group(2.57±0.50kg),lower in mild preeclampsia group (2.25±0.70)and lowest in severe preeclampsia group(1.80±0.37).This difference was found to be statistically significant.
40% of normotensive women and 62.8% of preeclamptic women were primipara.

The rate of LSCS was higher amongst the patients with preeclampsia.72.8% of preeclamptic women underwent LSCS as compared to 47.1% of normotensive women.

Table 2:Comparison of CBC parameters between normal pregnancy,mild and severe preeclampsia

Name of the Variable	Control(C)	Mild(M)	Severe(S)	P(C+M)	P(C+S)	P(M+S)
Hemoglobin (g/dL)	9.61±1.17	10.94±1.46	11.13±2.53	0.000	0.046	0.797
Haematocrit	31.28±3.16	31.77±5.67	32.01±6.83	0.614	0.703	0.908
RDW	19.46±3.99	18.04±3.95	18.99±4.70	0.072	0.729	0.506
Absolute neutrophil count	10472± 3347.98	8580.85± 3648.49	10276.14± 4451.58	0.008	0.878	0.214
Absolute lymphocyte	2415.16± 876.08	2340.71± 804.27	2821.07± 1163.68	0.650	0.234	0.170

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count						
NLR	5±2.68	4.03±2.05	4.14±1.96	0.034	0.172	0.861
Platelets	249.70±72.37	231.17±87.35	231.71±87.39	0.255	0.48	0.984
PLR	118.92±58.62	109.02±51.88	97.49±61.56	0.358	0.246	0.536

In our study,NLR was significantly higher in normotensive women as compared to women with mild preeclampsia (5±2.68 vs 4.03±2.05,p=0.034) .But,the difference in NLR was not significant when compared between normotensive women and women with severe preeclampsia(5±2.68 vs 4.14±1.96,p=0.172)

Though the PLR was lowest in the group with severe preeclampsia as compared to normal group and mild preeclampsia group (97.49±61.56 vs 109.02±51.88 vs 118.92±58.62) ,the difference was not statistically significant

The Absolute neutrophil count was higher in normotensive women than in women with mild preeclampsia (10472±3347 vs 8580 ±3648) and this difference was statistically significant.But there was no difference in absolute neutrophil count between mild and severe group (8580±3648 vs 10276±4451).

The absolute lymphocyte count also did not show any statistical difference in values across the normal,mild and severe preeclampsia group(2415±876 vs 2340±804 vs 2821±1163)

The RDW was marginally higher in normotensive women than in women with mild and severe preeclampsia (19.4±3.9 vs 18.04±3.9 vs 18.9±4.7)but the difference was not statistically significant.

The platelet counts were marginally lower in patients with severe preeclampsia than in patients with mild preeclampsia and normal patients(231.71±87.39 vs 231.17±87.35 vs 249.70±72.37) but the difference was not statistically significant.

The Haemoglobin levels were significantly higher in the group with severe preeclampsia as compared to women with mild preeclampsia and normal BP (11.13 vs 10.94 vs 9.61)and the difference was statistically significant (p=0.046)

Discussion

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In our study,we found that the preeclamptic women delivered at an earlier gestational age and had lower birth weights .Similar results have been reported by other studies(10,11,12).

We found that the value of NLR was higher in the group with normal patients as compared to those with mild preeclampsia and this result was significant statistically.But,this was in contrast to several other studies where the values of NLR was found to be higher in preeclamptic patients. A study by Gogoi et al from Delhi has reported that inflammatory markers NLR was higher in women with pre-eclampsia at term(13).

We have not found any statistically significant relation between value of NLR in normotensive and preeclamptic women.A study from Turkey by Yucel,has reported similar findings where no significant differences in NLR was found between the normotensive and preeclamptic women (10).

In their study on systemic inflammatory response markers in preeclampsia,Cintesun et al too have found no statistically significant differences between normal pregnant women and preeclamptic women when values of NLR were compared(14)

In another study,Kurtoglu et al have found that though NLR in preeclamptic group was significantly higher than that of normotensive group , there was no statistically significant relationship between NLR and severity of preeclampsia(15).

Jing Wang et al in a study to assess the efficacy of blood cell parameters to diagnose preeclampsia ,found that pregnant women with preeclampsia had significantly higher NLR (16)

Kang et al in his study has found that NLR was higher in pregnant women with preeclampsia patients than in patients with normal Blood pressure(11).

Maennarts et al have found in their study that higher NLR in preeclampsia group as compared to the group with normal patients(12).

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L Hai et al in their mini review of clinical utility of NLR in preeclampsia have found inconsistent evidence regarding the association between preeclampsia and NLR ,which maybe because many of the studies are cross sectional or case control in design(17)

In our study,PLR was lower in preeclamptic women than in normotensive women but the effect was not statistically significant.

A study from Turkey by Yucel,has reported that PLR was significantly lower in preeclamptic women(10). Maennarts et al have also found lower PLR in preeclampsia group as compared to the group with normal patients in their study(12).But, Cintesun et al have found no statistically significant differences between normal pregnant women and preeclamptic women when values of PLR were compared(14).Kang et al have also found no significant statistical differences in PLR values between preeclampsia patients and healthy pregnant women(11)

In our study ,we found that the RDW was higher in patients with normal blood pressure than preeclamptic women. This was in contrast to findings of several other studies where the values of RDW were higher in preeclamptic women.Kurt Raziye et al have found in their study that RDW was significantly higher in the preeclampsia group as compared to group with normal blood pressure(18). Moreover, the same study has also reported that RDW levels were significantly increased in patients with severe preeclampsia when compared to the patients with mild preeclampsia(18).A metaanalysis by Ishag Adam et al has also reported that RDW levels were significantly higher in women with preeclampsia compared to controls and it was significantly higher in women with severe preeclampsia compared to those with mild preeclampsia (19).

There was no difference in absolute neutrophil count and absolute lymphocyte count in patients with mild and severe preeclampsia in our study. Cintesun et al too have found no statistically significant differences between normal pregnant women and preeclamptic women when values of absolute lymphocyte count and absolute neutrophil count were compared(14). Jing Wang et al have found that pregnant women with preeclampsia had significantly higher absolute neutrophil

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count as compared to normal ,pregnant women(16). Kang et al in his study has found that leukocyte and neutrophil counts were all higher in pregnant women with preeclampsia patients than in patients with normal blood pressure(11).

A comparative study of white cell parameters and platelet count by Chomaw et al has reported that Absolute Neutrophil count and neutrophil-to-lymphocyte ratio (NLR) were significantly increased while Absolute lymphocyte count (ALC) and platelet count (PTC) were significantly decreased in women with preeclampsia(20)
We have found significantly higher levels of hemoglobin in women with preeclampsia. In a study of maternal hemoglobin concentration in preeclamptic women,Amburgey et al have found that hemoglobin levels are significantly raised in women with preeclampsia as compared to women with healthy pregnancy(21).
In our study we have compared blood cell indices at the time of labour in women with normal pregnant patients and in those with preeclampsia.Studies comparing first trimester values of inflammatory markers have shown better predictive value for preeclampsia. A study conducted by Kirbas et al from Turkey has reported that PLR and NLR in the first trimester were significantly higher in the patients with severe preeclampsia compared to the patients with mild preeclampsia . These values were also found useful to predict the severity of preeclampsia(22).

Mehmet Bulbul et al have found that instead of a single measurement of CBC parameters, the changes that take place in the parameters over the trimesters are more important to predict severe preeclampsia(23)

Conclusion

We have not found any association between values of NLR ,PLR ,absolute lymphocyte and neutrophil count ,RDW and platelet count in healthy pregnant patients and preeclamptic patients.The association between NLR,PLR and other blood cell indices with preeclampsia remains inconsistent.Larger prospective studies ,preferably cohort studies with trimester wise follow up of patients is needed to prove an association,if any , between these inflammatory markers and preeclampsia.

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