

Leucocyte and Platelet Indices in Preeclampsia compared to Normotensive Pregnant Women



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Introduction

Preeclampsia and indices of peripheral blood cells:

- Preeclampsia affects 3-5% of all gestations & is associated with significant maternal and perinatal morbidity and even mortality.
- Excessive inflammation, platelet activation and abnormal immune responses are the key pathological events.
- Recently, studies have explored clinical utility of indices of systemic immune response and inflammation derived from peripheral blood cells. Some of these include-
 - Neutrophil-to-lymphocyte ratio (**NLR**), Monocyte-to-lymphocyte ratio (**MLR**), Platelet-to-lymphocyte ratio (**PLR**), and Platelet indices such as Mean Platelet Volume (**MPV**), Platelet distribution width (**PDW**).
- Being easily measurable, these have recently attracted much attention in preeclampsia. However, most studies are either retrospective or cross-sectional. None had prospectively evaluated these parameters at more than one-time point.
- Hence, this prospective study was conducted.

Objective

- Primary: To assess leucocyte and platelet indices (NLR, MLR, PLR, PDW, MPV) in preeclampsia compared to normotensive pregnant women.
- Secondary: To correlate their levels with severity of preeclampsia.

Methods

- Study Design:** Prospective comparative observational study
- Registered with Clinical Trial registry of India CTRI/2020/09/027531
- Subjects:** Total 80 women were recruited after taking ethical approval:
- Group-1 (n=20): Pregnant women diagnosed as preeclampsia (ACOG criteria).
- Group-2 (n=60): Gestational age matched normotensive controls
- Exclusion criteria (for both groups): Chronic hypertension, overt diabetes, GDM-A2, renal disease, ischaemic heart disease, fever within previous one week, evidence of infection, collagen vascular disorder, autoimmune disorders.
- Work up:** Detailed history and examination was done.
- 3 ml venous blood drawn for baseline CBC for leucocyte and platelet indices. Participants were followed in antenatal clinic (cases 2-weekly, controls 2-4 weekly or earlier if required, till delivery)
- Sampling:** CBC repeated at 28, 32, 36 weeks and at delivery for both cases and controls. Last sample was taken on day of delivery, but before induction of labour or before shifting for caesarean. Among controls the last sample was taken at admission for delivery.
- Primary Outcome Measure:** NLR, MLR, PLR, PDW, MPV levels at recruitment and at delivery.
- Data analysis** done statistical software STATA version 17.0.
- Student t-test, non parametric Mann Whitney U test were applied as required.

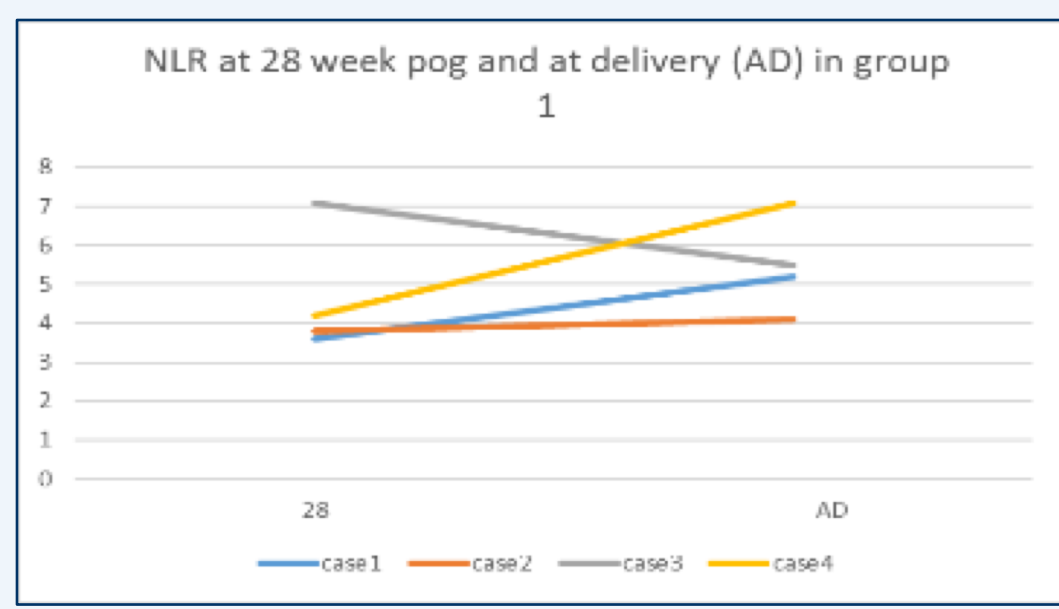
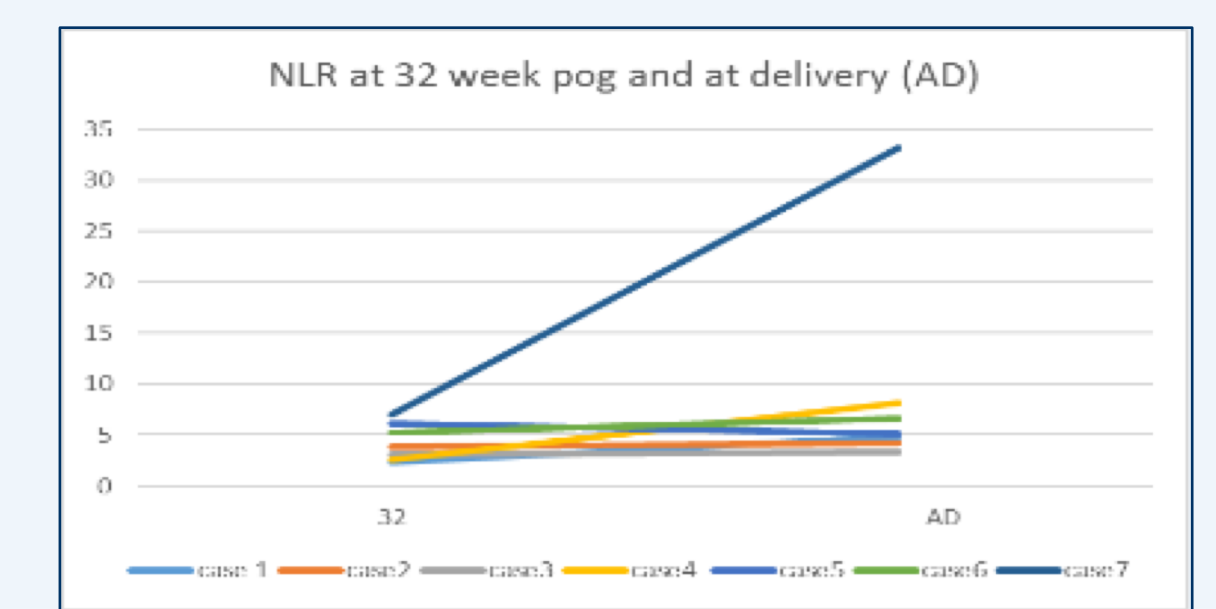
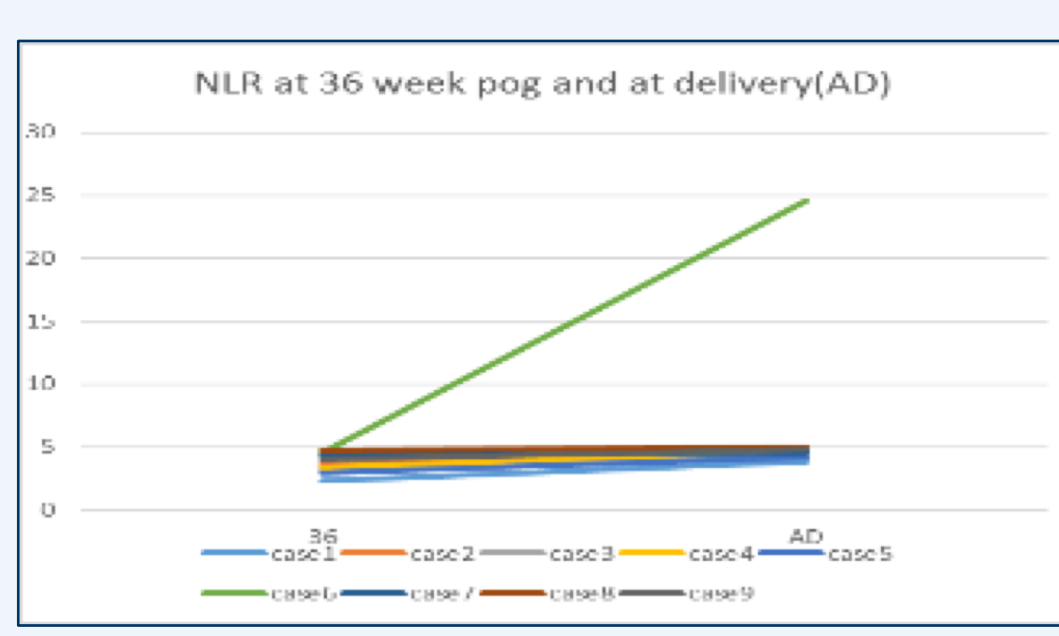
Results

- Baseline patient characteristics were comparable in both groups.
- In Group-1 (n=20), preeclampsia was diagnosed at 28 weeks in 4 patients 32 weeks in 7 patients 36 weeks in 9 patients
- Gestational age when these women delivered was also variable. Hence, study parameters were analysed in 3 subgroups according to gestation at diagnosis in addition to overall analysis.
- Primary Outcome: **The most consistent changes were observed in NLR.**

NLR		Group 1		Group 2		P Value
		N	Median (IQR)	N	Median (IQR)	
At baseline	Overall	20	3.84 (3.11-4.68)	60	3.65 (3.10-4.40)	0.796
	28 weeks	4	4.01 (3.68-6.35)	12	3.52 (3.22-3.66)	0.077
	32 weeks	7	3.85 (2.58-6.13)	60	3.65 (2.99-4.45)	0.967
	36 weeks	9	3.58 (3.04-4.49)	57	3.54 (2.99-4.12)	0.995
Delivery		20	4.88 (4.30-6.38)	60	3.66 (2.52-4.46)	0.001

- NLR in group 1 was higher at all gestations compared to controls.
- There was 27.1% increase in median NLR from baseline to delivery in group-1 versus no change in group 2
- Increase in NLR at delivery was significant in severe preeclampsia compared to preeclampsia without severe features (p =0.020)
- The patients who had steep rise in NLR had adverse outcomes compared to patients with not so steep rise.

Figure shows trend of NLR values from baseline to delivery in three subgroups



- Two patients in **group 1** had very high NLR of 33.2 and 24.6 on the day of delivery, both patients had eclampsia
- Rise in NLR was more than 200% in three patients (2 developed eclampsia, 1 had features of impending eclampsia)

Other Haematological markers:

- Median baseline MLR and PLR were comparable. Overall, no change was observed in MLR in group-1, 19% reduction was observed in group-2 at delivery. MLR was increased in the above three patients (75% rise in one and >300% rise in other two patients), but not all women with drastic increase in MLR had composite adverse outcome.
- In group-1, PLR was lower in early onset preeclampsia but was higher in late onset preeclampsia. PDW was lower in group-1 than controls. MPV was inconsistent between preeclampsia and controls.
- Whereas no consistent change was found in PLR, MPV and PDW were also variable when assessed in individual patients.
- Preeclampsia with severe features
- Out of total 20 preeclampsia patients in group-1, 8 (40%) had preeclampsia with severe features. This included 2(10%) patients who developed eclampsia and one who had features of impending eclampsia..
- There was significant difference in between birth weight of group 1 and group 2.

Discussion

Etio-pathogenesis of Preeclampsia:

Marked increase in leucocyte counts and modulation of neutrophil function towards greater production of superoxide than nitric → inflammation → platelet activation, vasoconstriction, endothelial dysfunction → end-organ ischemia → clinical manifestations of preeclampsia. Platelet activation manifests as low platelet count and high mean platelet volume MPV.

Neutrophil-to-Lymphocyte ratio (NLR):

- Reported as a predictor of severity of preeclampsia. Wang et al. 2019

Platelet-to-Lymphocyte ratio (PLR):

- An intensified state of platelet activation is reported even before the onset of PE and hence this can be used as a screening test for preeclampsia .

Monocyte-to-Lymphocyte Ratio (MLR):

A subclinical indicator of inflammation and is a prognostic factor for several diseases. In cancer, low MLR is associated with longer relapse-free survival time, indicating that MLR level can reflect body's immune status. Monocyte Infiltration suggests chronic inflammation.

Mean Platelet Volume (MPV):

- MPV is increased in PE, due to thrombocyte activation and aggregation.
- MPV is representative of an increase in megakaryocyte production in bone marrow, secondary to thrombocytopenia, and depends on severity of inflammatory response.

Platelet Distribution Width (PDW):

- An indicator of platelet distribution size and increases in platelet activation. Significantly increased PDW and plateletcrit reported in preeclampsia and is associated with severity.

Summary of studies on NLR in preeclampsia:

Studies	Sample size	Preeclampsia Median (IQR) or Mean ± SD	Controls Median (IQR) Mean±SD	P-value	Study Conclusion
Yucel et al, 2017 Retrospective	Mild PE - 27 Severe PE - 82 Controls - 110	3.68 (2-14.5) 3.94 (1.71-17.25)	3.57 (10-11.08.7)	0.707	No significant difference in NLR
Serin et al, 2016 Case control study	Mild PE - 37 Severe PE - 40 Controls - 37	5.68 ± 3.1 (mild + severe PE)	3.9±2.3	0.017	High in PE Higher in severe PE than mild PE Positive correlation with proteinuria (r= 0.319)
Gogoi et al, 2019 Cross sectional study	PE - 67 Control - 67	6.8 ± 7.6	3.0±0.98	0.001	NLR higher in PE
Mannaerts et al, 2019 Retrospective	PE- 164 Controls- 1886	3.08 ± 1.07	2.81±0.95	0.173	NLR higher in PE compared to controls
Wang et al, 2019 Retrospective study	PE- 367 (162 mild, 205 severe) Controls - 172	6.80 ± 2.13	6.16±1.51	<0.01	NLR >4.182 was cut off for severity and adverse neonatal outcome
Present study Prospective study	Total PE 20 Mild-12 Severe 8 Controls 60	At diagnosis 3.84 (3.11 - 4.68)	At recruitment 3.65 (3.10 - 4.40)	0.796	NLR higher in PE. Increased at delivery. Steep rise in pts developing eclampsia

Conclusion

Among all five study parameters, NLR levels were significantly high in preeclampsia with severe features compared to preeclampsia without severe features. NLR values were higher in preeclampsia both at diagnosis and at delivery compared to controls, with steep rise in patients who developed eclampsia or impending eclampsia. PLR was lower in early onset preeclampsia. Hence, these simple, inexpensive, complete blood count based tests can be offered even in low resource setting and have potential to be used for prognostication of preeclampsia.