# Correlation of Umbilical Artery Doppler Indices and Neutrophils to Lymphocyte Ratio, Platelet to Lymphocyte Ratio, Red Cell Distribution Width, Mean Platelet Volume to the Severity of Preeclampsia

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**Abstract**

Study Objective To explore the relationship among umbilical artery Doppler indices and certain hematological parameters (NLR, MPV, PLR and RDW), and the severity of preeclampsia. Methods This was a prospective cross-sectional study. Nine hundred and fifty pregnant women were included and divided into severe preeclampsia group (200), non-severe preeclampsia group (250) and control group (500). Umbilical artery Doppler indices as well as the hematological parameters were measured. Neonates were assessed as regards APGAR score at 1 and 5 minutes and neonatal birth weight. Results Umbilical artery RI and PI showed positive correlation with SBP (r=0.156 and 0.218, P value=0.019 and 0.002, respectively). Each of the UA RI, PI and S/D were significantly negatively correlated with AFI, APGAR 1 minute, APGAR 5 minute and NBW ( RI correlations: r= -0.572, P value <0.001: r = - 0.319, P value <0.001: r= -0.357, P value <0.001; r 0.357, P value <0.001; r= - 0.596, P value <0.001, respectively; PI correlations: r= -.0397, P value <0.001; r= -0.288, P value <0.001; r= -0.304, P value <0.001; r= -0.426, P value <0.001, respectively; SD correlations: r= -0.525, P value <0.001; r= -0.405, P value <0.001; r= -0.463, P value <0.001; r= -0.466, P value <0.001, respectively). NLR showed significant negative correlation with APGAR score at 1 minute and NBW (r= -0.162, P value=0.022; r= -0.237, P value = 0.001). Conclusion UA Doppler indices correlate with the severity of preeclampsia and the neonatal outcome. Neutrophils to lymphocytes ratio is the only hematologic parameter that correlates with neonatal outcome.

**Keywords:** *Severe preeclampsia, Umbilical artery, Doppler indices, Hematological parameters, APGAR score at 1 and 5 minutes, Neonatal birth weight.*

## INTRODUCTION

Preeclampsia is a pregnancy-related condition that can affect almost any organ in the body. While preeclampsia is much more than just hypertension during pregnancy with proteinuria, the presence of proteinuria is still an important objective diagnostic criterion [1].

Preeclampsia is described as an increase in systolic blood pressure of 140 mm Hg or diastolic blood pressure of 90 mm Hg on two different measurements taken at least 4-6 hours apart in a pregnant woman after 20 weeks of pregnancy with proteinuria of 0.3 gram in a 24-hour urine sample or a protein to creatinine ratio of 0.3 or a persistent urine dipstick reading of +1 or greater [2].

Doppler ultrasound is a useful method for studying fetal circulation and can provide important information about fetal health and prognosis. It is used for fetal monitoring in pregnancies complicated with intrauterine growth restriction (IUGR) to minimize the risk of perinatal death and long-term morbidity, and it can also be used as a guide to the optimize the timing of delivery [3].

Doppler ultrasound can also be used to determine fetal well-being in cases of preeclampsia, IUGR, and to predict perinatal mortality and long-term morbidity [3].

The red cell distribution width (RDW) is a parameter that is normally measured as part of a complete blood count using a fully automated hematology analyzer. RDW is an anisocytosis marker (red cell size variation). RDW has been shown to have a high sensitivity for detecting anemia and can indicate early changes in red blood cells that are accompanied by iron deficiency anemia [4].

Platelet indices, including mean platelet volume (MPV), platelet distributed width (PDW), and plateletcrit (PCT), are other examples of non-invasive biomarkers that can be tested easily and at low cost to assess disease status [5].

In non-pregnant patients, a clear link between RDW and MPV and hypertension has been identified. However, few trials in patients with preeclampsia have been conducted, and the findings have been contradictory [6].

In this study we tried to explore the relationship among umbilical artery Doppler indices and certain hematological parameters (NLR, MPV, PLR and RDW), and the severity of preeclampsia.

**Patients and Methods**

This prospective cross-sectional study was conducted in the Obstetrics and Gynecology Department of Kasr Alainy Hospital. The study population were recruited in the period from May 2017 to January 2019, in which, a total of 950 pregnant women between 18 and 40 years were included with singleton living fetus, term pregnancy (⩾ 37 weeks’ gestation), pregnant women having mild or severe preeclampsia comprised the cases group and normotensive healthy pregnant women comprised the control group.

Exclusion criteria included patients with any sign or symptom of active infection (pain, fever, or vaginal discharge), pregnant women with preexisting renal disease, bronchial asthma requiring steroidal treatment, chronic hepatitis, anticoagulant drug use history, history of oral contraceptive use (up to 6 months prior to pregnancy), smoking, diagnosed immune thrombocytopenic purpura (ITP), gastrointestinal or hematological disease, multiple gestations. Patients with gestational diabetes mellitus and suspected or diagnosed congenitally anomalous fetus were also excluded.

A total of 950 pregnant patients were included in the study and were divided into the following groups:

Group A: 200 pregnant women with severe preeclampsia.

Group B: 250 pregnant women with mild (non-severe) preeclampsia.

Group C: 500 normotensive pregnant women as a control group

Non severe Preeclampsia was defined as new onset of blood pressure ⩾140/90 mm Hg on more than two readings taken 6 hours apart after 20 weeks gestation, combined with proteinuria ⩾0.3 g/24 hours, but not meeting the standards for severe preeclampsia.

Severe preeclampsia was defined as: Blood pressure ⩾ 160/110 mm Hg, Thrombocytopenia (platelet count ⩽ 100,000 / microliter), impaired liver function as indicated by abnormally elevated liver enzymes, severe persistent right upper quadrant or epigastric pain unresponsive to medications and not accounted for by other diagnosis, or both, progressive renal insufficiency ( serum creatinine greater than 1.1 mg/dL), pulmonary edema and new onset of cerebral or visual disturbances as severe persistent headache, blurring or loss of vision.

All patients were subjected to the following:

Informed verbal consent was obtained from all women included in the study.

Full medical and obstetrical history gestational age in weeks was calculated from the first day of the last regular menstrual period and confirmed or modified by first trimesteric ultrasound measurements of crown rump length.

General, abdominal and obstetrical examination were done.

Abdominal ultrasound Trans-abdominal obstetric ultrasound examination using a Medison X6 (Medison Co., Ltd., Seoul, Korea) machine equipped with a 4–7 MHz trans-abdominal probe (3D4-7EK) for confirmation of the gestational age, presentation, exclusion of congenital anomalies, fetal biometry, amniotic fluid index (AFI) and estimated fetal weight (EFW). Calculation of EFW was based on Hadlock formula which utilizes the measurements of biparietal diameter, abdominal circumference and femur length. Umbilical artery Doppler indices were measured [systolic/diastolic ratio (S/D), pulsatility index (PI) and resistance index (RI)].

Laboratory investigations Urine analysis, complete blood count, coagulation profile and liver and kidney functions tests.

Venous blood sample Venous blood was withdrawn into three vacutanors: serum for testing liver and kidney functions, sodium citrate containing vacutanor for coagulation testing and an EDTA containing vacutanour for performing complete blood count with differential.

Complete blood count with differential It was used for testing the required hematological parameters: [neutrophils to lymphocytes ratio (NLR); platelets to lymphocytes ratio (PLR); red cell distribution width (RDW) and mean platelet volume (MPV)]. Red cell distribution width (RDW), mean platelet volume (MPV) was measured using the automated blood cell counter (Abbott Cell Dyn 1800, Abott Park,IL 60064, USA). Platelets, neutrophils and lymphocytes were counted and the counts were verified through the stained film. These counts were used to calculate the previously mentioned ratios namely: NLR and PLR. Results were recorded for each patient.

After Delivery the neonates were assessed by a neonatologist as regards gender, neonatal birth weight and Apgar score at 1 and 5 minutes.

Statistical analysis Data were statistically described in terms of mean standard deviation (SD), median and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of numerical variables between the study groups was done using one way analysis of variance (ANOVA) test with posthoc multiple 2- group comparisons. For comparing

categorical data, Chi-square (2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between various variables was done using Pearson moment correlation equation for linear relation of normally distributed variables and Spearman rank correlation equation for non-normal variables/non-linear monotonic relation.

**Results**

Different groups were compared as regards patient's clinical characteristics, laboratory investigations, ultrasonographic findings and neonatal outcome as well as examining the correlation between umbilical artery Doppler indices (RI, PI and SD) and the hematologic parameter (RDW, N/L, P/L and MPV) with preeclampsia severity.

When comparing control and non-severe preeclampsia groups, statistically significant differences were encountered as regards gestational age (GA) at delivery, SBP and DBP. Gestational age at delivery was higher in the control group than that in the non-severe group (38.14 ± 1.127 weeks and 37.92 ± 0.825 weeks respectively, P value 0.013).

Upon comparing severe and non-severe preeclampsia groups as regards laboratory investigations, urinary albumin, Hb level, HCT, RDW and NLR were all higher in severe preeclampsia group rather than non-severe preeclampsia group (urinary albumin=2.83 ± 0.796 VS 2.35 ± 0.674, P value <0.001; Hb level =11.160 ±1.5765 gm% VS 10.800± 1.3740 gm %, P value 0.030; HCT=34.500 ± 6.6824 % VS33.352 ± 4.1220 %, P value 0.030; RDW=16.769 ± 2.7465 % % VS 15.932 ± 2.5088, P value 0.003; NLR = 3.892 ± 4.3203 VS 3.179± 1.8652, P value 0.030), as shown in table (1).

Comparing the severe preeclampsia group with the non-severe preeclampsia group regarding the ultrasonographic findings, gestational age by ultrasound was significantly lower in the severe preeclampsia group than that in the non-severe preeclampsia group (35.68± 2.059 weeks VS 36.59± 1.682 weeks, P value<0.001). Umbilical artery RI, PI and S/D were significantly elevated in severe preeclampsia group compared to the non-severe preeclampsia group (RI=0.6936 ± 0.11855 VS 0.6662 ± 0.09581, P value 0.013; PI=1.2134 ± 0.34971 VS 1.0991 ± 1.09, P value<0.001; S/D=2.6654 ± 0.62654 VS 2.2972 ± 0.59145, P value<0.001). AFI was significantly lower in severe preeclampsia group compared to non-severe preeclampsia group (6.72 ± 3.276 cm VS 9.16 ± 3.590 cm, P value<0.001).

Upon comparing neonatal outcome findings between the severe preeclampsia group and the control group, statistically significant differences were noted for APGAR 1min, APGAR 5min and NBW as they were all significantly lower in the severe preeclampsia group than those in the control group (APGAR 1min = 4.55± 0.742 VS 5.03± 0.865, P value <0.001; APGAR 5min = 7.78 ± 0.974 VS 8.32 ± 0.840, P value <0.001; NBW= 2573.75 ± 538.328 gm VS 2808.50 ± 508.153 gm, P value<0.001).This was illustrated in tables (1).

**Table (1) Comparison of clinical characteristics, laboratory investigations and U/S findings among study groups**

| | Control (mean ± SD) (n= 500) | Non- severe (mean ± SD) (n= 250) | P Value (Control VS Non-severe) | Severe (mean ± SD) (n=200) | P Value (Control VS Severe) | P Value (Severe VS Non-severe) |
|---|---|---|---|---|---|---|
| **Age (years)** | 29.66 ± 6.150 | 29.88 ± 5.923 | 1.00 | 29.73± 6.239 | 1.00 | 1.00 |
| **Gravidity** | 2.60 ± 1.807 | 2.68 ± 1.902 | 1.00 | 2.69± 2.318 | 1.00 | 1.00 |
| **Parity** | 2.14 ± 1.379 | 2.13 ± 1.386 | 1.00 | 2.00± 1.854 | 0.830 | 1.00 |
| **Gestational Age (weeks)** | 38.14 ± 1.127 | 37.92 ± 0.825 | 0.013 | 37.57± | <0.001 | <0.001 |
| **BMI (kg/m²)** | 30.73±N16.469 | 32.13± 22.907 | 0.845 | 30.27± 0.691 | 1.00 | 0.726 |
| **SBP (mm Hg)** | 119.57± 43.367 | 150.72± 3.652 | <0.001 | 173.65± 12.073 | <0.001 | <0.001 |
| **DBP (mmHg)** | 74.17± 9.733 | 99.54± 4.938 | <0.001 | 109± 12.532 | <0.001 | <0.001 |
| **Urinary albumin (+)** | 0.03± 0.243 | 2.35± 0.674 | <0.001 | 2.83± 0.796 | <0.001 | <0.001 |
| **Hb (gm%)** | 10.701± 1.4771 | 10.800± 1.3740 | 1.00 | 11.160± 1.5765 | 0.001 | 0.030 |
| **HCT (%)** | 33.350± 3.9296 | 33.352± 4.1220 | 1.00 | 34.500± 6.6824 | 0.010 | 0.030 |
| **RDW (%)** | 15.991± 2.7015 | 15.932± 2.5088 | 1.00 | 16.769± 2.7465 | 0.002 | 0.003 |
| **NLR** | 3.379± 2.6119 | 3.179± 1.8652 | 1.00 | 3.892± 4.3203 | 0.105 | 0.030 |
| **PLR** | 106.06± 63.813 | 103.14± 61.915 | 1.00 | 103.44± 77.846 | 1.000 | 1.000 |
| **MPV (fL)** | 12.109± 1.8684 | 12.246± 2.1960 | 1.00 | 12.444± 1.7256 | 0.115 | 0.842 |
| **GA U/S (weeks)** | 36.86± 1.663 | 36.59± 1.682 | 0.159 | 35.68± 2.059 | <0.001 | <0.001 |
| **UA RI** | 0.6491± 0.09605 | 0.6662± 0.09581 | 0.087 | 0.6936± 0.11855 | <0.001 | 0.013 |
| **UA PI** | 1.0616± 0.23914 | 1.0991± 1.09 | 1.00 | 1.2134± 0.34971 | <0.001 | <0.001 |
| **UA S/D** | 2.2824± 0.54643 | 2.2972± 0.59145 | 1.00 | 2.6654 ± 0.62654 | <0.001 | <0.001 |
| **AFI (cm)** | 9.55± 3.924 | 9.16± 3.590 | 0.532 | 6.72± 3.276 | <0.001 | <0.001 |
| **EFW (gram)** | 2954.04± 495.496 | 2867.33± 503.087 | 0.086 | 2785.11± 557.313 | <0.001 | 0.271 |
| **APGAR 1min** | 5.03± 0.865 | 4.89± 0.763 | 0.080 | 4.55± 0.742 | <0.001 | <0.001 |
| **APGAR 5min** | 8.32± 0.840 | 8.26± 0.855 | 1.000 | 7.78± 0.974 | <0.001 | <0.001 |
| **NBW (gram)** | 2808.50± 508.153 | 2704.40± 508.305 | 0.027 | 2573.75± 538.328 | <0.001 | 0.023 |

Neutrophils to lymphocytes ratio was positively correlated with DBP (r=0.182, P value= 0.010) and negatively correlated with APGAR 1 min (r=-0.162, P value=0.200) and NBW (r=-0.237, P value=0.001), as shown in table (2).

**Table (2) Correlation of NLR to SBP, DBP, urine albumin, AFI, APGAR 1 min, APGAR 5 min and NBW in cases with severe preeclampsia**

| | Item | Correlation coefficient (r) | P value |
|---|---|---|---|
| **NLR** | **SBP** | -0.022 | 0.761 |
| | **DBP** | 0.182 | 0.010 |
| | **Urinary albumin** | 0.123 | 0.084 |
| | **AFI** | -0.139 | 0.050 |
| | **APGAR 1 min** | -0.162 | 0.022 |
| | **APGAR 5 min** | -0.097 | 0.173 |
| | **NBW** | -0.237 | 0.001 |

Platelets to lymphocytes ratio was not correlated with preeclampsia severity (SBP, DBP and urinary albumin), AFI or neonatal outcome (APGAR 1 min, 5min and NBW), table (3)

**Table (3) Correlation of PLR to SBP, DBP, urine albumin, AFI, APGAR 1 min, APGAR 5 min and NBW in cases with severe preeclampsia**

| | Item | Correlation coefficient (r) | P value |
|---|---|---|---|
| **PLR** | **SBP** | -0.109 | 0.124 |
| | **DBP** | -0.004 | 0.956 |
| | **Urinary albumin** | 0.065 | 0.363 |
| | **AFI** | -0.049 | 0.495 |
| | **APGAR 1 min** | -0.118 | 0.097 |
| | **APGAR 5 min** | -0.132 | 0.063 |
| | **NBW** | -0.071 | 0.319 |

Also, RDW and MPV were not correlated with the severity of preeclampsia (SBP, DBP, urine albumin), AFI or neonatal outcome (APGAR 1 min, APGAR 5 min and NBW), as summarized in tables (4).

**Table (4) Correlation of RDW to SBP, DBP, urine albumin, AFI, APGAR 1 min, APGAR 5 min and NBW in cases with severe preeclampsia**

| | Item | Correlation coefficient (r) | P value |
|---|---|---|---|
| **RDW** | **SBP** | 0.001 | 0.987 |
| | **DBP** | -0.099 | 0.162 |
| | **Urinary albumin** | 0.117 | 0.100 |
| | **AFI** | -0.036 | 0.611 |
| | **APGAR 1 min** | -0.110 | 0.120 |
| | **APGAR 5 min** | -0.098 | 0.166 |
| | **NBW** | -0.058 | 0.417 |

## Discussion

The percentage of primigravidas was 22% (44 out of 200) in severe preeclampsia group and 21.2% (53 out of 250) in the non-severe preeclampsia group. This doesn't agree with other studies published in literature.

Long reported in 1979 that the frequency of preeclampsia was 14.1 percent in primigravidas and 5.7 percent in multiparas in a study of 26,209 patients. This disagreement with our results might probably be due to racial and geographic characteristic differences among study populations [7].

The mean gestational age at delivery was 37.57 ± 0.69 weeks in severe preeclampsia group, 37.92 ± 0.825 weeks in non-severe preeclampsia group and 38.14 ± 1.127 weeks in control group.

NLR and PLR are non-specific indicators of systemic inflammatory response (SIR) obtained from CBC in peripheral blood [8]. The ratio of neutrophils, which represent the active non-specific inflammatory mediator that initiates the first line of defence , to lymphocytes, which represent the regulatory or protective portion of inflammation, is known as the neutrophil-lymphocyte ratio (NLR) [9].

In the present study, NLR was significantly higher in patients with severe preeclampsia than non-severe pregnancies, but did not exhibit significant difference between the patients with preeclampsia (either severe or non-severe) and normal pregnancies.

Yavuzcan indicated that NLR was not significantly different in patients with severe preeclampsia and healthy pregnant women, which was similar to the current study results [10].

In contrast to our study, Oylumlu demonstrated that increased levels of NLR were independently associated in patients with PE compared to healthy pregnancies [11].

In the light of the literature and the present study, although NLR has been proposed as a new indicator of SIR and its predictive and prognostic values in much different pathology have been demonstrated in the previous studies, the current study assumes that NLR role is still unclear to be a predictor for existing disease or for severity in preeclampsia.

Platelets and lymphocytes are crucial blood components for immune surveillance, and the platelet-lymphocyte ratio (PLR) represents important cytokine-dependent immune responses [12].

In the current study we did not observe any difference as regards PLR between the preeclamptic patients and the healthy pregnancies or between severe preeclampsia and non-severe preeclampsia. Similar to our findings, Yavuzcan stated that PLR was not significantly different between patients with preeclampsia and stable pregnancies [10].

MPV is a parameter that measures platelet activity and can rise or fall depending on the intensity of the inflammatory response [13]. In the current study we did not observe significant differences as regards MPV between normal pregnancies and preeclamptic patients or any relation between the MPV and the severity of preeclampsia. Mehmet in his study in 2016 stated that MPV was higher in preeclamptic patients than normal; he did not observe any relation between the MPV and the severity of PE. So, the data on the significance of MPV in the literature are contradictory.

In the current study, Hb and HCT were significantly higher in patients with severe preeclampsia than those of non-severe preeclampsia or normal pregnancy. This can be attributed to the marked hemoconcentratin encountered with preeclampsia.

Umbilical artery Doppler indices (RI, PI, S /D) are useful diagnostic tools to identify hemodynamic consequences caused by preeclampsia

In the current study, there was significant elevation in umbilical artery indices in severe preeclamptic pregnant patients in comparison with women with normal pregnancy and non-severe preeclampsia.

Also, in agreement with our study, in a cross-sectional analysis on 125 normal pregnancy and 62 preeclamptic women at 31 – 40 weeks of gestation, Özeren in 1999 found that the umbilical artery PI and S/D ratio were higher in cases of IUGR due to preeclampsia than in cases of normal pregnancies [14].

Our findings are also in line with the study performed by Chen which showed not only a higher PI in preeclamptic patients in comparison to normal pregnant women but also a significantly greater PI in severe cases of preeclampsia than non-sever cases [15].

In the current study, amniotic fluid index was lower in pregnant women with severe preeclampsia rather than those with non-severe

preeclampsia or normal pregnancy. This comes with agreement with Bansal whose study noted that mean amniotic fluid index (AFI) in preeclampsia group was lower than control group. This can be attributed to placental insufficiency secondary to preeclampsia [16].

In the current study, Apgar score at 1, 5 minutes were significantly lower in neonates born to mothers with severe preeclampsia in comparison with those with non-severe preeclampsia and normal pregnancy.

This comes in agreement with the study done by Özeren in 1999 who described that 5 minutes Apgar score was significantly lower in cases with severe preeclampsia [14].

In the current study, we observed that the overall mean birth weight was markedly lower among babies born to mothers with preeclampsia compared to those without. Furthermore, NBW was significantly lower in women with severe preeclampsia compared to those with non-severe preeclampsia. This was in agreement with a study done by Xiong in 2000 which described lower NBW in preeclamptic women compared to normotensive pregnant women [17].

In current study, umbilical artery RI and PI showed positive significant correlation with SBP. RI was positively correlated with urinary albumin. This comes in disagreement with Joern in 1999 who concluded that the severity of the maternal disease is not necessarily correlated with the degree of the pathological changes in the Doppler sonographic blood flow patterns [18].

Each of the umbilical artery RI, PI and S/D were significantly negatively correlated with AFI, APGAR 1 minute, APGAR 5 minute and NBW.

Upon correlating the hematological parameters (NLR, PLN, RDW, MPV) with preeclampsia severity, in terms of SBP, DPB and urinary albumin and neonatal outcome as regard APGAR 1 minute, APGAR 5 minutes and NBW, only NLR showed significant negative correlation with APGAR score at 1 minute and NBW. No previous studies in the literature described any relation between NLR and the previously mentioned signs of preeclampsia severity or neonatal outcome. This study was prospective with lager sample size in comparison to previously held studies and provided correlation of the hematological parameters with the neonatal outcome.

The conclusion of this study is that UA Doppler indices correlate with the severity of preeclampsia and the neonatal outcome. Neutrophils to lymphocytes ratio is the only hematologic parameter that correlates with neonatal outcome.

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