# Predictive value of Lipocalin 2 and hyperuricemia on maternal and fetal outcome in pre-eclampsia

**Diagnostic Study**

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## ABSTRACT

**Background**: Pre-eclampsia is a complex hypertensive syndrome that originates in early pregnancy and leads to considerable maternal and fetal morbidity and mortality. Lipocalin 2 is low in healthy human tissue but increased in pathological conditions following endothelial cell injury. Women with pre-eclampsia showed elevated uric acid level in the maternal blood.

**Objective**: To assess the predictive value of Lipcalin 2 and hyperuricemia on the severity of pre-eclampsia and on maternal and fetal outcome.

**Patients and Methods**: Sixty women enrolled in the present study were forty affected by preeclampsia and 20 women with uncomplicated pregnancies formed the control group. All women included in the study were subjected to; complete history taking; clinical and blood pressure evaluation; measurements of biochemical parameters and evaluation of maternal and fetal well-being.

**Results**: Thirty-two of hypertensive women were mild pre-eclampsia having blood pressure ≥140/90mmHg but less than 160/110mmHg. Eight cases were severe pre-eclampsia with the presence of blood pressure ≥160/110 mmHg. All hypertensive women showed statistically significant increased biochemical parameters compared to control "$p<0.001$". Lipocalin 2 and serum uric acid levels in the studied group showed a positive correlation with various biochemical parameters and hyperuricaemia showed a good relation with the pathogenesis of the maternal and fetal manifestations.

**Conclusion**: Lipocalin 2 could be used as a sensitive indicator of severity of preeclampsia. On the other hand hyperuricaemia showed a good relationship with fetal outcome in hypertensive disorder of pregnancy, identifying those fetuses that are likely to have Intra Uterine Growth Retardation and high perinatal mortality.

**Key Words:** Biochemical parameters, hyperuricaemia, lipocalin 2, predicting, pre-eclampsia

**Received:** 11 February 2017, **Accepted:** 26 May 2017

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**ISSN:** 2090-7265, November 2017, Vol.7, No.4

## INTRODUCTION

Hypertensive disorders of pregnancy (HDP) remain one of largest single causes of maternal and fetal morbidity and mortality 1. Approximately 30% of HDP cases were due to chronic hypertension, while 70% of cases were due to gestational hypertension/preeclampsia [2].

Pregnancy may induce hypertension in women who are normotensive before pregnancy and may aggravate hypertension in those who are hypertensive before pregnancy [3,4].

Pre-eclampsia is a multisystem disorder that complicates about 3–8% pregnancies. It is characterized by high blood pressure of 14090/ mmHg or more along with proteinuria (>0.3gm/24 hours urine collection) or any derangement in platelet count, liver enzymes or renal function tests that occur after 20 weeks of gestation [5]. The incidence is high in developing countries due to hypoproteinemia, malnutrition and poor obstetric facilities. Overall, 10–15% of maternal deaths are directly associated with pre-eclampsia and eclampsia [6].

The risk of pre-eclampsia is two to five times more in women with maternal history of this disorder. The incidence of pre-eclampsia is high in healthy nulliparas ranging from 3% to 7% [7] than in nultiparas ranging from 1% to 3% [8].

Preeclampsia affects multiple organ systems and can lead to severe renal, hepatic, neurological, and cardiopulmonary complications and adverse perinatal outcomes (preterm birth, intrauterine growth restriction, and death) [9]. The major risk to the fetus results from decreased placental perfusion leading to decreased blood supply of oxygen and nutrients necessary for fetal growth and wellbeing [5].

 *DOI: 10.21608/ebwhj.2018.5579*

Lipocalin-2 (LCN2), also known as oncogene 24p3 or neutrophil gelatinase-associated lipocalin (NGAL), is a protein that in humans increased at the end of the second trimester in women who subsequently developed pre-eclampsia compared to the control group [10].

Women with preeclampsia showed elevated uric acid level in maternal blood, presumably due to decreased renal urate excretion. Various studies conducted to find out the relationship between elevated serum uric acid level and preeclampsia [11].

Therefore, in the present study, we compared serum LCN2 and uric acid levels in women with pre-eclampsia with those of uncomplicated pregnancies to identify the potential association with the severity of preeclampsia and adverse maternal and perinatal outcomes.

## PATIENTS AND METHODS

This study was conducted in, Tanta university Hospital over 9 months duration from June 2015 to March 2016, after research ethical committee approval and informed written consent taken from subjects included in this study (30256 /04/ 15). Forty women with pre-eclampsia having high blood pressure of 14090/ mmHg or more (group 1) and 20 healthy pregnant non hypertensive women (control group 2) were analyzed. This control group was well matched with the cases for maternal age, parity and gestational age. The inclusion criteria were: age range between 20 -35 years; gestational age (22 -38weeks), women with pre-eclampsia having high blood pressure of 14090/ mmHg or more. The exclusion criteria were: Subject refusal, woman suffering from gestational hypertension, chronic kidney disease, active urinary tract infection, chronic hypertension, diabetes mellitus, chronic liver disease, cardio vascular disease and those who had infective and neoplastic pathology. All women included in the study (cases and control) on time of hospital admission were subjected to; complete history taking; clinical and blood pressure evaluation; measurements of blood urea; serum creatinine; serum uric acid; serum Lipocalin 2 by ELISA and 24 h collection of urine for protein level estimation . All patients were assessed for maternal and fetal well-being. The data were collected and analyzed. Mild preeclampsia was defined as blood pressure ≥14090/mmHg but less than 160110/mmHg with proteinuria ≥300mg/24hours. Severe preeclampsia was defined as presence of blood pressure ≥160110/ mmHg with urinary protein excretion of ≥2.0gm/24hours or any of these, oliguria or <400ml urine/24hours, visual disturbances, serum creatinine ≥1.2mg/dl, platelets less than 100,000/mm3, microangiopathic hemolysis. HELLP syndrome was defined as elevation of liver enzymes (AST more than 70 IU/L), hemolysis (Lactate dehydrogenase "LDH" more than 600 IU/L), and low platelet counts (≤100,000/mm3). Acute renal failure was defined as elevated creatinine of ≥ 1.5 fold from the baseline or oliguria of ≥24 hrs. Proteinuria was defined as 24 hours urinary protein excretion of ≥300 mg [12,13].

Measurement of blood pressure was done 4 hourly, in patients of preeclampsia and control in the right arm in the supine position. Korotkoff V sounds were taken for measurement of diastolic blood pressure by a mercury sphygmomanometer [13]. 5 ml of venous blood samples were collected from the cases and controls and allowed to clot. Samples were then centrifuged and 2ml of serum for routine investigation and 1ml were stored at - 20°c till assay of serum lipocalin 2 by enzyme linked immunosorbent assay (ELISA) technique, through using sandwich enzyme-linked Immunosorbent Assay Kit. (Uscn Life Science Inc. China). Serum uric acid estimation was done by nephalometry, blood urea estimation; serum creatinine estimation was done by jaffess method; and sulfosalicylic acid test used for urinary protein estimation in 24 h collection of urine [13].

Alfa methyldopa was given for mild preeclampsia which is a centrally acting belongs to category B drug and is safe for the mother and fetus. Calcium channel blocker with methyldopa was given in cases of severe preeclampsia and if blood pressure wasn't controlled we add B blocker which is FDA category C drug. All patients were followed up to 6 weeks postpartum.

### Statistical analysis

Statistical analysis was carried out using the software program Anova one-way unstacked. Quantitative data were presented as mean and standard deviation. Pearson correlation for measuring covariance of two variables divided by the product of their standard deviations measures the strength of a linear association between two variables and is denoted by r. The Receiver Operator Characteristic (ROC) curve was used for prediction of pre-eclampsia using sensitivity, specificity, accuracy and the predictive values (positive and negative).

Sensitivity: probability that the test results will be positive when the disease is present (true positive rate, expressed as a percentage); Specificity: Probability that the test results will be negative when the disease is present (true negative rate, expressed as a percentage); Positive Predictive value (PPV: probability that the disease is present when the test is positive); Negative Predictive value (NPV: probability that the disease is present when the test is negative) and accuracy is the ratio of the true positive and true negative on all patients. Result was considered significant at a *P value of <0.05* and highly significant at a *P value of P<0.01*.

## RESULTS

Analysis was carried out on 40 cases of pre-eclampsia where; 32 were mild pre-eclampsia (80%),

eight cases were severe pre-eclampsia (20%) and 20 controls. The maximum number of cases was in the age range of 25- 30 years, of them 75% were in mild preeclampsia group and 50% in severe preeclampsia. Also, the maximum number of cases was primigravida in either mild (53.125%) or severe (50%) preeclampsia; or controls 50%. The mean period of gestational age was nearly similar in pre-eclampsia cases and control (p=0.968).

Mean systolic blood pressure among mild preeclampsia group was 145.31+ 4.81mm Hg, in severe preeclampsia group 167. 50+ 7.56 mmHg, compared to control group100.50 + 8.26 mm Hg, with statistically high significant difference between pre-eclampsia cases and control *(p<0.0001)*. Also, there was statistically high significant difference between mean diastolic blood pressure in pre-eclampsia cases and control *(p<0.0001)*; and in urine output/24hrs *(p<0.001)*. None of the control or mild pre-eclampsia cases showed oliguria (>400ml/24hrs). Oliguria was found in 25% of severe preeclampsia cases as shown in Table (1).

All biochemical parameters in pre-eclampsia whether mild or severe showed high significant increase *(p<0.001)* compared with control group. Lipocalin 2 and serum uric acid levels were significantly increased with severity of disease in studied group (Table 2). None of the controls showed proteinuria <300mg/24hours, in the group of mild preeclampsia 53.12% cases had proteinuria ≥300mg/24hours and 46.88% cases had proteinuria ≥2gm in 24 hours. In the group of severe preeclampsia 35.12% cases had proteinuria ≥2gm in 24 hours and 62.50% cases showed proteinuria >4gm/24hours. This indicating increased intensity of proteinuria with the severity of disease (Table 3). Prediction of preeclampsia was done on the basis of serum LCN2 using calculation of ROC curve and area under ROC curve. Sensitivity and specificity of serum Lipocalin2 using a cut off value of 480 pg/ml, for the diagnosis of preeclampsia was found to be 100% and 100% respectively, using 95% confidence interval.

The positive predictive value was 100%, negative predictive value was 100%, area under curve (AUC) was 1.0 and accuracy index was 100 % (Tables 4, 5 and Fig. 1). There was positive correlation of lipocalin2 with various studied biochemical parameters, showing high significant correlation with uric acid and 24 hrs protein in urine sample *(p<0.001)* (Table 6 and Fig. 2).

Examined Cases (control; mild pre-eclampsia and severe pre-eclampsia) had 12 fetuses with intra uterine growth retardation (IUGR); 5 preterm, 1died (IUFD) the rest (42) were in good condition some of them need only incubation for increased bilirubin level. One case of control had CS (5%), while 10 (32%) cases of mild pre-eclampsia and 4cases (50%) of severe pre-eclampsia delivered by CS. Twenty four women of mild pre-eclampsia were in good condition with no complications after delivery and 8 showed complications. All women of severe pre-eclampsia showed complications and some of them were treated in ICU. Maternal and fetal complications were correlated with severity of disease in various studied groups (Table 7) and with Lipocalin2 and uric acid levels (Table 8).

**Table 1 :** Demographic data of the studied groups

| Groups | | Control | Mid Preeclampasia | Severe Preeclampasia | P Value |
|---|---|---|---|---|---|
| Number | | 20 | 32 | 8 | |
| Age years | <25 | 4 (20%) | 6 (18.75%) | 3 (37.5%) | 0.494 |
| | 25-30 | 14 (70%) | 24 (75%) | 4 (50%) | |
| | >30 | 2 (10%) | 2 (6.25%) | 1 (12.5%) | |
| Mean | | w | 26.80+ 3.22 | 27.25+ 4.26 | 0.924 |
| Gravida | 1 | 10 (50%) | 17 (53.125%) | 4 (50%) | 0.217 |
| | 2 | 6 (30%) | 8 (25%) | 2 (25%) | |
| | 3 | 3 (15%) | 5 (15.6%) | 1 (12.5%) | |
| | 4 | 1 (5%) | 2 (6.25) | 1 (12.5%) | |
| Mean Period of gestation | | 29.45 + 5.20 | 29.68+ 5.25 | 30.00+ 5.78 | 0.968 |
| SBP(mmHg) | Range | 90-110 | 140-155 | 160-180 | <0.0001 |
| | Mean + SD | 100.50 + 8.26 | 145.41+ 4.77 | 167. 50+ 7.56 | |
| DBP(mmHg) | Range | 60-80 | 90-115 | 100-120 | <0.0001 |
| | Mean + SD | 70.90+ 5.13 | 92.47+ 5.52 | 108.13 + 7.53 | |
| Urine output | >400ml/24hrs | 20 (100%) | 32 (100%) | 6 (75%) | <0.001 |
| | <400ml/24hrs | | | 2(25%) | |

SD = standard deviation; BP= blood pressure; SBP=systolic blood pressure; DBP=Diastolic blood pressure

**Table 2:** Biochemical parameters of the studied groups

| Items | Control(N=20) | Mid Preeclampasia (N=32) | Severe Preeclampasia (N=8) | P Value |
|---|---|---|---|---|
| Hb (gm/dl)<br>Range<br>Mean + SD | 9-11.8<br>10.38+ 0.96 | 6.8-11<br>9.17+ 1.18 | 6.8-10.4<br>9.05+ 1.03 | 0.001 |
| Platelet count (thousands/mm3)<br>Range<br>Mean + SD | 150-285<br>210.25+ 40.99 | 80-200<br>118.00 + 31.36 | 85-110<br>98.75 + 11.57 | <0.001 |
| Serum uric acid (mg/dl)<br>Range<br>Mean + SD | 3.40-4.5<br>2.88+ 0.56 | 4.3-7.8<br>6.69+ 1.08 | 6.5-11.1<br>8.65+ 1.49 | <0.001 |
| Serum urea (mg/dl)<br>Range<br>Mean + SD | 18-45<br>26.45 + 6.64 | 15-60<br>37.91 + 16.07 | 35-90<br>54.38 +18.98 | <0.001 |
| Serum Creatinine (mg/dl)<br>Range<br>Mean + SD | 0.70- 1.3<br>0.81 0.15 | 0.70-2.8<br>1.66+ 0.68 | 0.90-2.9<br>2.26+ 0.66 | <0.001 |
| S. Bilirubin (mg/dl)<br>Range<br>Mean + SD | 0.4 – 0.9<br>0.52+ 0.14 | 0.5-1.5<br>1.06+ 0.33 | 0.6-2<br>1.66+ 0.45 | <0.001 |
| S AST (U/L)<br>Range<br>Mean + SD | 12-34<br>20.95+ 7.49 | 22-38<br>30.56+ 6.03 | 28-48<br>40.00+ 8.21 | <0.001 |
| Urinary protein level in 24 hrs (mg/24hr)<br>Range<br>Mean + SD | 90 – 125<br>104.70+ 9.7 | 330 – 3400<br>1639.9 + 873.0 | 3000-5600<br>4290.0 + 921.0 | <0.001 |
| Serum lipocalin 2 )ng/ml)<br>Range<br>Mean + SD | 200– 440<br>293 + 69 | 480-7320<br>4975+ 1909 | 7320-10755<br>9597+ 1309 | <0.001 |

AST=Aspartate aminotransferase

**Table 3**: Proteinuria in various studied groups

| Protein level in 24 hrs (mg/24hr) | Control (N=20) | Mild preeclampsia (N=32) | Severe preeclampsia (N=8) |
|---|---|---|---|
| <300mg | 20 (100%) | 0 (0.00%) | 0 (0.00%) |
| >300mg | 0 (0.00%) | 17 (53.12%) | 0 (0.00%) |
| >2gm | 0 (0.00%) | 15 (46.88%) | 3 (35.12%) |
| >4gm | 0 (0.00%) | 0 (0.00%) | 5 (62.50%) |

**Table 4:** Test Result Variable(s): Lipocalin2

| | | | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|
| Area | Std. Error(a) | Asymptotic Sig.(b) | Lower Bound | Upper Bound |
| 1.000 | .000 | .000 | 1.000 | 1.000 |

a -Under the nonparametric assumption. b - Null hypothesis: true area = 0.5

**Table 5**: Area under the curve, sensitivity, specificity, predictive values and accuracy

| | Cutoff | AUC | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|---|
| Lipocalin 2 | 480 | 1.0 | 100 | 100 | 100 | 100 | 100 |

AUC =Area under Curve; PPV=positive predictive value; NPV=negative predictive value.

**Table 6:** Correlation between Lipocalin2 and biochemical parameters (uric acid, urea, creatinine, serum Bilirubin, AST and 24 hrs protein in urine sample) in pre-eclampsia cases

| | Lipocalin 2 | |
|---|---|---|
| | r. | p |
| Uric acid | 0.503 | 0.001* |
| Urea | 0.309 | 0.052 |
| Creatinine | 0.450 | 0.004* |
| Bilirubin | 0.383 | 0.015* |
| AST | 0.313 | 0.049* |
| 24 hrs protein in urine sample | 0.674 | 0.001* |

AST=Aspartate aminotransferase

**Table 7**: Correlation between fetal and maternal outcome in various studied groups

| Fetal outcome | Control (N=20) | Mild preeclampsia (N=32) | Severe preeclampsia (N=8) |
|---|---|---|---|
| Bad | 1 (5%) | 10 (31.25%) | 7(87.5%) |
| Good | 19(95%) | 22(68.75%) | 1(12.5%) |
| Maternal outcome | | | |
| No complications | 20(100%) | 24 (75%) | 0 (0.00%) |
| Complications | 0 (0.00%) | 8 (25%) | 8 (100%) |
| Pulmonary edema admitted to ICU | 0 (0.00%) | 3(9.4%) | 1 (12.5%) |
| Accidental hemorrhage | 0 (0.00%) | 4(12.5%) | 2 (25%) |
| HELLP | 0 (0.00%) | 1 (3.12%) | 2 (25%) |
| ARF | 0 (0.00%) | 0 (0.00%) | 1 (12.5%) |
| Eclampsia | 0 (0.00%) | 0 (0.00%) | 2 (25%) |

ICU= Intensive care unit; HELLP= Hemolysis, Elevated Liver Enzymes, Low Platelets; ARF =Acute Renal Failure

**Table 8**: Correlation of Lipocalin2 and serum uric acid with maternal and fetal outcome

| Items | Fetal outcome | | Maternal out come | |
|---|---|---|---|---|
| Lipocalin2 (n=60) | Bad (n= 18) | Good (n=42) | Complications (n=16) | No Complications (n=44) |
| <440 ng/ml | 1 IUGR (5.55%). | 19 (45.23%) | 0 (0.00) | 20 (45.45%) |
| >480 ng/ml | 7IUGR (38.88%)<br>3Preterm (16.66%) | 22 (45.23%) | -3Pulmonary edema (18.75%)<br>-4Accidental hemorrhages (25%)<br>-1 HELLP (6.25%) | 24(54.54%) |
| >7320 ng/ml | 4 IUGR (22.22%)<br>2Preterm (11.11%)<br>1 IUFD (5.55%) | 1 (9.52%) | -1Pulmonary edema (6.25%)<br>-2Accidental hemorrhages (12.5%)<br>-2 HELLP (12.5%)<br>-1 ARF (6.25%)<br>-2 Eclampsia(12.5%) | (0.00) |
| Uric acid | Bad (n= 18) | Good (n=42 | Complications (n=16) | No Complications(n=44) |
| <5 mg/dl | 1 IUGR (5.55%)<br>1Preterm (5.55%) | 27 (64.29%) | • -1 Pulmonary edema (6.25%) | 28 (63.63%) |
| <5 mg/dl | 5 IUGR (27.77)<br>2preterm (11.11%) | 9 (21.42%) | -2 Pulmonary edema (12.5%)<br>-3 accidental hemorrhages (18.75%)<br>• -1 HELLP (6.25%) | 12(27.27%) |
| >7 mg/dl | 6 IUGR (33.33%)<br>2preterm (11.11%)<br>1 IUFD (5.55%) | 6 (14.29%) | -1Pulmonary edema (6.25%)<br>-3 Accidental hemorrhages (18.75%)<br>-2 HELLP (12.5%)<br>-1 ARF (6.25%)<br>-2 Eclampsia(12.5%) | 4 (9%) |

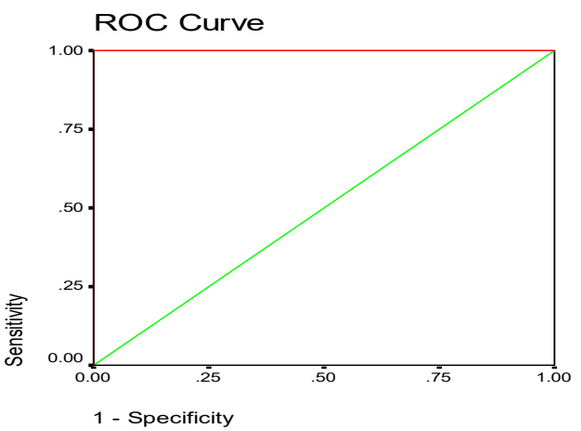


**Fig. 1**: ROC curve analysis showing sensitivity 100%, specificity 100% at cutoff value 480 ng/ml of Lipocalin2.

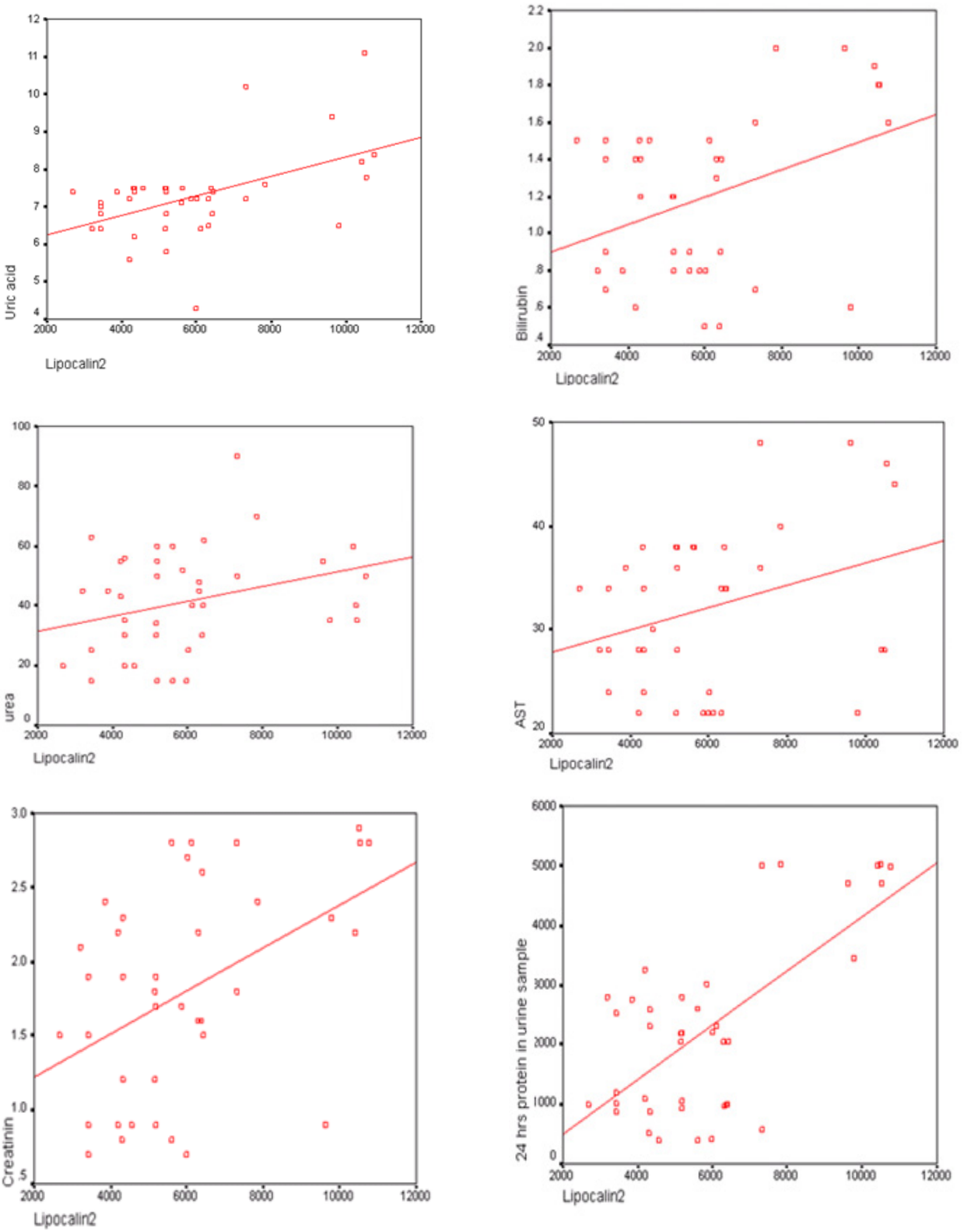


**Fig. 2:** Positive correlation of Lipocalin2 with various studied biochemical parameters (uric acid, urea, creatinine, serum bilirubin, AST and 24 hrs protein in urine sample) in pre-eclampsia cases

## DISCUSSION

Pre-eclampsia a hypertensive disorders complicating pregnancy (HDP) is a major disease which seriously endangers the safety of mother and fetus during pregnancy. Pre-eclampsia affects approximately 28- percent of pregnancies worldwide and is considered as the major cause of maternal and fetal morbidity and mortality [14].Thus major efforts are being made to identify effective biomarkers for the risk assessment and disease management.

An ideal biomarker of pre-eclampsia is the one that would allow an accurate prediction during the first trimester as it offers a wide range for effective treatment that may help in complete recovery or reduce the severity of disease [15].

The present study mainly focuses on biomarker Lipocalin-2 and hyperuricemia in predicting the severity of pre-eclampsia and maternal and perinatal outcome. Analysis was carried out on 40 women with pre-eclampsia (32 mild pre-eclampsia and eight severe pre-eclampsia) and 20 healthy pregnant non hypertensive women. In this study the maximum number of cases was in the age range of 25 -30 years and primigravida with nearly similar mean period of gestational age in all studied cases (preeclampsia and control). Our findings coincided with those of Rosaria *et al* [16] who found that age wise distribution, in cases of preeclampsia was similar to controls. We found statistically significant difference between mean systolic and diastolic blood pressure in pre-eclampsia cases and control, where maximum severity was found in the group of severe preeclampsia *(p<0.0001)*. Similarly, Sachan *et al* [17] showed that preeclampsia in systolic blood pressure and diastolic blood pressure was positively correlated with severity of disease.

In the present study none of the control or mild pre-eclampsia cases showed oliguria (>400ml/24hrs). Oliguria was found in 25% of severe preeclampsia cases, with statistically significant difference between preeclampsia cases and control *(p<0.001)*. This was comparable to study carried out by various authors[18] in which oliguria was found in 9.43% women with hypertensive disorders of pregnancy, Sachan *et al* [17] showed oliguria in 18.07% cases of severe preeclampsia and 20% cases of eclampsia, with statistically significant difference *(p<0.001)*.

We detected in the present study significantly increasing mean levels of serum urea and creatinine in preeclampsia cases as compared to controls *(p<0.001)*, and constantly increasing levels with the severity of disease, as had been found by Gebhard *et al* [19]. In the group of severe preeclampsia 35.12% cases had proteinuria ≥2gm in 24 hours and 62.50% cases showed proteinuria >4gm/24hours. This indicating increased intensity of proteinuria with the severity of disease.

In our study, ROC curve of Lipocalin 2 using a cut-off value of 480 ng/ml showed 100%sensitivity, 100% specificity of serum, for the diagnosis of preeclampsia at 95% confidence interval. The positive predictive value was 100%, negative predictive value was 100%, area under curve (AUC) was 1.0 and accuracy index was 100%. These results slightly differed, from those obtained by Sachan *et al*[17] who detected positive predictive value 98.58%, negative predictive value 90.63%, area under curve (AUC) was 95.72% and accuracy index was 97.11% at a cut-off value of 545 ng/ml.

Serum Lipocalin 2 showed positive correlation with serum urea (r =0.309), serum creatinine (r=0.450) and proteinuria. Therefore, Lipocalin2 might be considered a novel biomarker for early prediction of preeclampsia and also useful in assessment of disease severity. D'Anna *et al* [20] showed positive correlation of Lipocalin2 with the systolic, diastolic blood pressure and with proteinuria and considered Lipocalin2 a reliable biomarker for early prediction of pre-eclampsia.

In the present study, 24(40%) women went into spontaneous labor while the rest were induced. Among those who delivered, 15 (25%) underwent caesarean section while the remaining delivered vaginally. The most common complication associated with pre-eclampsia in this study was accidental hemorrhage 6(15%). Other complications associated were pulmonary edema 4 (10%), HELLP 3 (7.5%), eclampsia 2(5%) and ARF1 (2.5). There were no cases of maternal mortality. Such findings were comparable with those of Aabidha *et al* [21] who showed in their study that the most common complication in pre-eclampsia was antepartum hemorrhage (13.97%), followed by post partum hemorrhage (10.75%) and eclampsia (5.37%), with no maternal mortality.

The most common neonatal complications met with in the present study of pre-eclampsia cases were IUGR 12 (30%), preterm 5 (12.5%) IUFD 1(2.5). Aabidha *et al* [21] showed that pre-maturity (23.65%) was the most common neonatal complications followed by low birth weight (7.52%) and intra uterine growth restriction (9.67%) in their studied pre-eclampsia cases. These neonatal complications could result from decreased placental perfusion in pre-eclampsia leading to decreased blood supply of oxygen and nutrients necessary for fetal growth and wellbeing.

In the present study, serum uric acid levels were significantly raised in preeclampsia cases as compared to controls *(p<0.001)*. The values of serum uric acid when compared with mean serum Lipocalin 2 level, showed a positive correlation (r=0.503). These results coincided with those of Sachan *et al* [17] .

However, results are controversial regarding hyperuricemia. Several studies said that serum uric acid is a reliable predictor of preeclampsia [22], others suggested that the predictive value of serum uric acid is relatively poor for diagnosis and prognosis of preeclampsia [23,24]. Therefore, prediction of preeclampsia could be better evaluated by serum Lipocalin 2 which is a sensitive indicator of severity of the disease. The time of onset of pre-eclampsia is of great importance in determining the final outcome of fetus because the only treatment for such disorder is earliest delivery that may endanger fetal outcome.

Various studies suggested that elevated serum uric acid in pregnancy is not only a valuable biomarker for pre-eclampsia, but it may also have a contributory role in pathogenesis of maternal and fetal manifestation [25]. We found in our study increased fetal complications with rising of serum uric acid level from 5 mg/dl to more than >7 mg/dl. This coincided with some studies suggesting that the degree of elevation of serum uric acid level correlates with the severity of maternal syndrome and fetal morbidity [26] .Tejal and Astha[27] showed that the time at which serum uric acid concentration begins to rise is an approximate indicator of the time of onset of the preeclampsia. They showed the value of measuring serum uric acid in hypertensive pregnancy between 24 to 32 weeks of gestation. Low values indicate a good prognosis for the fetus. Rising or high values at this time indicate high-risk cases which are better managed and treated in hospital.

## CONCLUSION

In conclusion, Lipocalin2 could be considered a novel biomarker for early prediction of preeclampsia and also useful in assessment of disease severity. Measurement of serum uric acid is recommended beside other biomarkers used in pre-eclampsia as it is of great diagnostic and prognostic value for fetus to assess the severity of morbidity, identifying those fetuses that are likely to have IUGR and high perinatal mortality. Additional studies involving larger populations are needed to further investigate the role of these biomarkers in the diagnosis and prediction of preeclampsia to avoid serious maternal complications and give the best possible chance of fetal survival.

## CONFLICT OF INTEREST

There is no conflict of interest.

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