

DIAGNOSTIC UTILITY OF LACTATE DEHYDROGENASE-TO-PLATELET AND TRIGLYCERIDE-TO-HDL CHOLESTEROL RATIOS IN PREECLAMPSIA: A CROSS-SECTIONAL OBSERVATIONAL STUDY

R. Niranjani¹, D. Sobana², R. Nishanth³, M. Saradha⁴

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Corresponding Author:
Dr. R. Niranjani,
Email: niranraju20@gmail.com

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¹Assistant Professor, Department of Biochemistry, Government Thoothukudi Medical College, Thoothukudi, Tamil Nadu, India.

²Assistant Professor, Department of Biochemistry, Government Thoothukudi Medical College, Thoothukudi, Tamil Nadu, India.

³Senior Data scientist, Great Learning, Chennai, Tamil Nadu, India.

⁴Professor & HOD, Department of Biochemistry, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India.

ABSTRACT

Background: Preeclampsia (PE) involves endothelial dysfunction, platelet activation, and atherogenic dyslipidemia. The LDH-to-Platelet ratio (LPR) and Triglyceride-to-HDL Cholesterol ratio (THR) combine routinely measured biochemical parameters into integrated indices reflecting cellular injury and dyslipidemia. **Aim:** To evaluate the diagnostic utility of the Lactate dehydrogenase-to-Platelet ratio (LPR) and Triglyceride-to-HDL Cholesterol ratio (THR) in Preeclampsia (PE), and their ability to discriminate PE with and without severe features. **Materials and Methods:** This cross-sectional observational study included 150 singleton pregnancies beyond 20 weeks of gestation, classified according to ACOG criteria into normotensive pregnancy (n=50), PE without severe features (n=50), and PE with severe features (n=50). Serum LDH, Triglycerides and HDL cholesterol were measured using automated methods and platelet counts using an automated hematology analyzer. LPR was calculated as LDH (U/L)/platelet count ($\times 10^3/\mu\text{L}$) and THR as triglycerides/HDL cholesterol (mg/dL). ROC analysis was performed for PE versus normotensive pregnancy and severe versus non-severe PE. **Results:** LDH, Triglycerides, LPR and THR were higher and Platelet count and HDL cholesterol lower in PE than in normotensive pregnancy (all $p < 0.001$). Median LPR was 0.66, 1.55 and 2.09 in normotensive, non-severe PE and severe PE, respectively. For PE versus normotensive pregnancy, LPR showed an AUC of 0.979 (95% CI 0.940–1.000) and THR 0.940 (0.900–0.980), both $p < 0.001$. For severe versus non-severe PE, LPR showed an AUC of 0.655 (0.547–0.763; $p = 0.008$) and THR 0.677 (0.572–0.782; $p = 0.002$). **Conclusion:** LPR and THR showed strong discrimination of PE from normotensive pregnancy but modest discrimination between severe and non-severe PE. They may serve as adjunctive biochemical indices; their role in severity assessment requires validation in larger, independent cohorts.

INTRODUCTION

Preeclampsia is a multisystem hypertensive disorder of pregnancy characterized by new-onset hypertension after 20 weeks of gestation accompanied by proteinuria and/or maternal organ dysfunction. The disorder arises from complex interactions among abnormal placentation, placental malperfusion, oxidative and inflammatory stress, angiogenic imbalance and maternal endothelial

dysfunction. Its clinical phenotype is heterogeneous, and biochemical abnormalities may accompany progression from preeclampsia without severe features to disease with severe features.^[1-5]

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme present in multiple tissues and erythrocytes. Increased serum LDH activity can accompany cellular injury, tissue hypoxia and hemolysis. Several studies have reported higher LDH concentrations in Preeclampsia, particularly in severe disease, although

LDH is nonspecific and should be interpreted in the context of clinical and laboratory findings.^[6-11] Platelet count may decrease in Preeclampsia as a consequence of Platelet activation, endothelial injury and increased consumption; a systematic review and meta-analysis has confirmed lower Platelet counts in women with preeclampsia compared with normotensive pregnant women.^[12]

Combining LDH and Platelet count into a calculated LDH-to-Platelet ratio (LPR) may provide a composite representation of two routinely available biochemical and hematological variables. The ratio, however, should be regarded as a calculated index rather than a direct measurement of hemolysis, endothelial injury or coagulopathy. Its performance is necessarily influenced by the behaviour and measurement characteristics of both component variables.

Pregnancy is also accompanied by physiological changes in lipid metabolism. Several observational studies and meta-analyses have reported higher Triglyceride and Total Cholesterol concentrations and, particularly later in pregnancy, lower HDL Cholesterol concentrations among women with Preeclampsia.^[13-17] The Triglyceride-to-HDL Cholesterol ratio (THR) integrates two components of this lipid pattern and has therefore been explored in the present study as a calculated biochemical index.

Previous investigations have generally evaluated individual LDH, Platelet or lipid measurements, while evidence concerning combined LPR and THR in established preeclampsia remains limited. The present study therefore evaluated LPR and THR across normotensive pregnancy, PE without severe features and PE with severe features, and assessed their discriminatory performance for PE versus normotensive pregnancy and for severe versus non-severe PE.

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional observational study was conducted by the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology at Government Tirunelveli Medical College, Tirunelveli. The study was undertaken over a period of one year. The study protocol was approved by the Institutional Ethics Committee of Government Tirunelveli Medical College. Written informed consent was obtained from all participants before enrolment.

Study Population

A total of 150 singleton pregnancies beyond 20 weeks of gestation were included and classified according to ACOG criteria into three groups: normotensive pregnancy (n=50), Preeclampsia without severe features (n=50), and Preeclampsia with severe features (n=50).

Diagnostic Criteria

Normal Pregnancy Diagnosis: Based upon clinical and ultrasound evaluation, ensuring participants had no signs of hypertension or proteinuria

Participants were classified according to the American College of Obstetricians and Gynaecologists (ACOG) diagnostic framework.

Preeclampsia was defined by new-onset hypertension after 20 weeks of gestation, with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on two occasions at least 4 hours apart, accompanied by proteinuria or, in the absence of proteinuria, new-onset maternal organ dysfunction.

Proteinuria was defined as ≥ 300 mg protein in a 24-hour urine collection, a protein-to-creatinine ratio ≥ 0.3 , or a urine dipstick reading of 2+ when quantitative methods were unavailable.

PE with Severe features included systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg, platelet count $< 100,000/\mu\text{L}$, impaired liver function with transaminases at least twice the normal concentration and/or severe persistent right upper quadrant or epigastric pain, renal insufficiency with serum creatinine > 1.1 mg/dL or doubling of serum creatinine in the absence of other renal disease, pulmonary edema, or new-onset headache unresponsive to medication or visual symptoms.

Participants fulfilling diagnostic criteria for Preeclampsia but without any severe feature were classified as PE without severe features

Exclusion Criteria

Women with epilepsy, hemolytic anemia, multiple gestation, chronic hypertension, pre-existing or gestational diabetes mellitus, known renal or hepatic disease, or autoimmune disorders were excluded.

Sample Collection and Pre-analytical Processing

A detailed clinical history was recorded using a predesigned proforma. Five millilitres of venous blood were collected after an overnight fast. Blood collected for serum analysis was allowed to clot and serum was separated by centrifugation at 3000 rpm for 15 minutes. The separated serum was used for biochemical analysis. Platelet counts were performed on the hematology specimen using an automated Sysmex analyzer. Analytical measurements were performed using the same laboratory platforms throughout the study as applicable.

Biochemical Analysis

Serum LDH, serum Triglycerides, serum HDL Cholesterol and serum Total Cholesterol were analyzed using enzymatic methods on an Erba XL-640 Fully Automated Clinical Chemistry analyzer. Serum LDH activity was measured using the DGKC (German Society for Clinical Chemistry) method. The LDH method is based on the enzymatic conversion of pyruvate to lactate with concomitant oxidation of NADH, with the change in absorbance monitored photometrically. The laboratory reference interval used for serum LDH was 225–450 U/L. Values in healthy late pregnancy may fall slightly below general non-pregnant reference intervals; this reference interval was used for laboratory

interpretation of LDH and was not used as a diagnostic threshold for preeclampsia.

Serum Triglycerides were estimated by the glycerol phosphate oxidase-peroxidase (GPO-POD) enzymatic method. HDL cholesterol was estimated by a homogeneous direct method. Total Cholesterol was estimated by the Cholesterol oxidase-Peroxidase (CHOD-POD) enzymatic method. The analytical approach for LDH was consistent with established reference methodology for measurement of catalytic enzyme activity at 37°C.

Hematological Analysis

Platelet count was measured, expressed as $\times 10^3/\mu\text{L}$, using a Sysmex automated hematology analyzer.

Calculation of Ratios

LPR was calculated as: $\text{LPR} = \text{serum LDH (U/L)} \div \text{platelet count } (\times 10^3/\mu\text{L})$. THR was calculated as: $\text{THR} = \text{serum triglycerides (mg/dL)} \div \text{serum HDL cholesterol (mg/dL)}$.

Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. Blood pressure was recorded using standard clinical procedures, and proteinuria was assessed as part of the obstetric evaluation.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26. Continuous variables were assessed for distribution using the Shapiro–Wilk test and are presented as median with interquartile range (IQR) because the principal biochemical variables were not normally distributed. Comparisons across the three groups were performed using the Kruskal–Wallis test. Pairwise Mann–Whitney U tests with Bonferroni adjustment were used for post-hoc comparisons. Receiver operating characteristic (ROC) curves were generated for PE versus normotensive pregnancy and for severe versus non-severe PE. The area under the curve (AUC), 95% confidence interval, sensitivity and specificity at the maximum Youden-index cut-off were reported. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

The study included 150 participants, with 50 in each group. Serum LDH, serum Triglycerides, LPR and THR differed significantly across the three groups (all $p<0.001$). Platelet count and HDL cholesterol also differed significantly across groups ($p<0.001$). Median LPR was 0.66 (0.58–0.77) in normotensive pregnancy, 1.55 (1.29–2.32) in PE without severe features and 2.09 (1.53–2.91) in PE with severe features.

BMI did not differ significantly across the three groups ($p = 0.129$), whereas systolic and diastolic blood pressure differed significantly (both $p<0.001$). Post-hoc analysis showed that LPR differed significantly between all three pairwise group comparisons after Bonferroni adjustment (normotensive vs non-severe PE, adjusted $p<0.001$; normotensive vs severe PE, adjusted $p<0.001$; non-severe vs severe PE, adjusted $p=0.023$). THR differed significantly between normotensive and non-severe PE (adjusted $p<0.001$), normotensive and severe PE (adjusted $p<0.001$), and non-severe and severe PE (adjusted $p=0.007$). Although triglycerides differed significantly overall across the three groups, the pairwise comparison between non-severe and severe PE was not significant after Bonferroni adjustment (adjusted $p=1.00$).

For discrimination of PE from normotensive pregnancy, LPR showed an AUC of 0.979 (95% CI 0.940–1.000), with a Youden-index cut-off of 0.95, sensitivity 98% and specificity 98%. THR showed an AUC of 0.940 (95% CI 0.900–0.980), with a cut-off of 3.56, sensitivity 83% and specificity 92%.

For discrimination of severe versus non-severe PE, LPR showed an AUC of 0.655 (95% CI 0.547–0.763), with a Youden-index cut-off of 1.73, sensitivity 64% and specificity 64% ($p=0.008$). THR showed an AUC of 0.677 (95% CI 0.572–0.782), with a Youden-index cut-off of 3.83, sensitivity 70% and specificity 60% ($p=0.002$).

Table 1: Biochemical parameters and calculated indices. Data are presented as median (IQR)

Parameter	Normotensive (n=50)	PE without severe features (n=50)	PE with severe features (n=50)	p value
LDH (U/L)	195.00 (174.50–215.50)	354.00 (302.00–512.50)	451.00 (349.50–567.75)	<0.001
Platelets ($\times 10^3/\mu\text{L}$)	289.50 (267.75–340.00)	232.50 (217.75–245.75)	218.00 (212.25–244.50)	<0.001
†Triglycerides (mg/dL)	123.00 (119.00–137.00)	159.00 (154.00–168.00)	159.00 (153.00–167.00)	<0.001
HDL-C (mg/dL)	44.50 (42.00–46.00)	43.00 (41.00–45.00)	41.00 (39.00–42.00)	<0.001
LPR	0.66 (0.58–0.77)	1.55 (1.29–2.32)	2.09 (1.53–2.91)	<0.001
THR	2.84 (2.63–3.20)	3.73 (3.52–3.96)	3.95 (3.73–4.17)	<0.001

† Triglycerides differed significantly overall by Kruskal–Wallis testing, but the post-hoc comparison between PE without severe features and PE with severe features was not significant after Bonferroni adjustment (adjusted $p=1.00$). $\text{LPR} = \text{LDH (U/L)} \div \text{platelet count } (\times 10^3/\mu\text{L})$; $\text{THR} = \text{triglycerides (mg/dL)} \div \text{HDL-C (mg/dL)}$.

Table 2: Clinical characteristics of the study groups. Data are presented as median (IQR). P-values are from the Kruskal–Wallis test

Parameters	Normotensive (n=50)	PE without severe features (n=50)	PE with severe features (n=50)	p value
BMI	23.22 (22.22–24.67)	24.02 (22.70–25.10)	24.24 (22.52–25.61)	0.129
SBP (mmHg)	116.00 (114.00–126.00)	146.00 (144.00–150.00)	164.00 (160.00–167.50)	<0.001
DBP (mmHg)	74.00 (72.00–76.00)	92.00 (90.50–94.00)	110.00 (104.50–112.00)	<0.001

Table 3: Receiver Operating Characteristic (ROC) curve analysis. Cut-offs correspond to the maximum Youden index in the present dataset and require independent validation

Diagnostic objective	Marker	AUC (95% CI)	Cut-off	Sensitivity	Specificity	p value
PE vs normotensive	LPR	0.979 (0.940–1.000)	0.95	98%	98%	<0.001
PE vs normotensive	THR	0.940 (0.900–0.980)	3.56	83%	92%	<0.001
Severe vs non-severe PE	LPR	0.655 (0.547–0.763)	1.73	64%	64%	0.008
Severe vs non-severe PE	THR	0.677 (0.572–0.782)	3.83	70%	60%	0.002

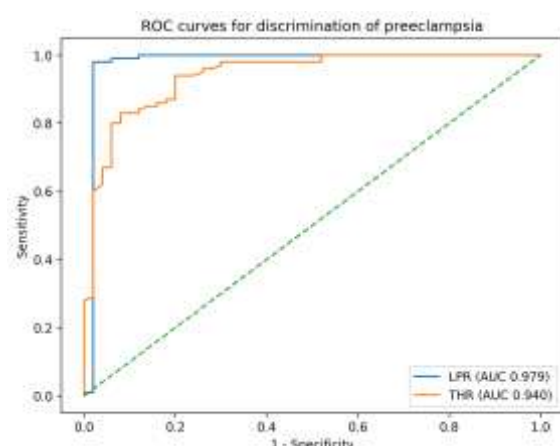


Figure 1: ROC curves demonstrating discrimination of preeclampsia from normotensive pregnancy by LPR and THR

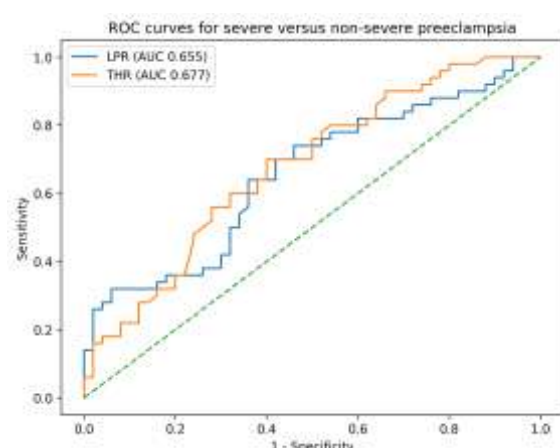


Figure 2: ROC curves demonstrating discrimination of severe preeclampsia from non-severe preeclampsia by LPR and THR

DISCUSSION

This study demonstrated that LPR and THR showed strong discrimination between Preeclampsia (PE) and normotensive pregnancy, whereas their ability to distinguish PE with severe features from PE without severe features was modest. This distinction is important because statistically significant differences across clinical groups do not necessarily translate into clinically useful discrimination between adjacent disease phenotypes.^[21–23]

Serum LDH reflects cellular injury and end-organ hypoperfusion resulting from intracellular hypoxia-induced enzyme leakage in preeclampsia, while reduced platelet counts reflect endothelial activation and platelet consumption.^[1,5,6,7] In the present study, LDH increased progressively and platelet counts decreased across clinical groups. LPR integrates these two parameters into a single calculated index. The AUC of 0.979 for PE versus normotensive pregnancy indicates strong discrimination. Jaleel and Baseer,^[6] and Qublan et al,^[7] reported associations between elevated LDH and preeclampsia severity and adverse pregnancy outcomes. More recently, Teklemariam et al. reported an AUC of 0.963 for LDH in discriminating preeclampsia from normotensive pregnancy.^[10] These findings support the relevance of LDH abnormalities in PE, although they do not constitute direct validation of LPR.

For severe versus non-severe PE, LPR showed only modest discrimination (AUC 0.655; 95% CI 0.547–0.763; $p=0.008$). This finding is consistent with the limited severity discrimination reported for other LDH-derived indices. Geyik Bayman et al. reported an AUC of 0.639 for the LDH/albumin ratio in distinguishing severe PE in a multicentre retrospective cohort.^[19] An important methodological consideration is that thrombocytopenia is itself an ACOG severe feature. Therefore, incorporation of platelet count into LPR may introduce criterion-

related bias when LPR is evaluated against a severity classification that includes platelet count. Accordingly, the present LPR severity finding should be interpreted as modest discriminatory performance rather than evidence of an independent severity marker.

Maternal dyslipidemia, characterized by accelerated systemic lipolysis, decreased lipolytic clearing, and endothelial dysregulation, has been associated with oxidative stress and abnormal placental vascular function in PE.^[5,13-17] In the present study, Triglycerides were higher and HDL cholesterol lower in PE than in normotensive pregnancy. These findings are consistent with studies by Enquobahrie et al,^[13] Wiznitzer et al,^[14] and Vrijkotte et al,^[15] which demonstrated associations between maternal lipid abnormalities and pregnancy complications. Ray et al,^[16] and Spracklen et al,^[17] also reported associations between maternal triglycerides, hyperlipidemia, and preeclampsia. A recent meta-analysis by Qin et al. similarly reported higher triglycerides and adverse lipid profiles among women with PE.^[20]

THR demonstrated strong discrimination for PE versus normotensive pregnancy (AUC 0.940; 95% CI 0.900-0.980), but only modest discrimination for severe versus non-severe PE (AUC 0.677; 95% CI 0.572-0.782; $p = 0.002$). Although triglycerides differed significantly overall among the three groups, the non-severe versus severe comparison was not significant after Bonferroni adjustment ($p = 1.00$). Thus, the observed THR separation appears to reflect the combined distribution of triglycerides and HDL cholesterol rather than a consistent triglyceride gradient between the two PE severity categories.

The study has limitations. Its single-centre, cross-sectional design and relatively small sample limit generalizability and preclude causal inference. Cut-offs were derived and evaluated in the same dataset and require independent validation. Potential confounding by gestational age, maternal characteristics, medication exposure, and metabolic factors cannot be excluded. In addition, incorporation of platelet count into LPR creates potential criterion-related bias in severity analysis. Therefore, LPR and THR should be regarded as calculated adjunctive biochemical indices rather than standalone severity tests.

CONCLUSION

LPR and THR demonstrated strong discrimination between Preeclampsia and normotensive pregnancy but only modest discrimination between PE with and without severe features. These ratios may serve as readily obtainable adjunctive biochemical indices reflecting combined laboratory abnormalities in PE. However, the observed cut-offs should not be adopted for routine clinical use without validation in larger, multicentre cohorts with independent

validation and appropriate adjustment for potential confounders.

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