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Original article

Role of serum high-sensitive C-reactive protein to predict severity of pre-eclampsia in a high-population resource-poor country: a prospective observational study

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Abstract

Objective: To determine the role of high-sensitive C-reactive protein (hsCRP) in predicting the severity of preeclampsia in a high-population, resource-poor country.

Patients and Methods: This prospective cohort study was conducted at the Department of Obstetrics and Gynaecology of Calcutta National Medical College, India, from March 2021 to September 2022. A total of 180 participants were divided into three equal groups: patients with severe preeclampsia and non-severe preeclampsia and healthy pregnant women.

Results: The levels of the biomarkers hsCRP and uric acid differed significantly between women with preeclampsia and healthy women, with cutoff levels of 3.72 mg/L and 5.15mg/dL, respectively, as determined using receiver operating characteristic (ROC) curve analysis. HsCRP was also able to differentiate severe preeclampsia from non-severe preeclampsia at a cutoff level ≥8.75 mg/L (high Youden index >0.6). However, uric acid levels failed to discriminate between pregnant women with severe and non-severe preeclampsia. Elevated hsCRP levels were strongly associated with low birth weight of newborns in pregnant women with pre-eclampsia and healthy control groups (P=0.001) and with disease severity (P<0.001), respectively.

Conclusions: HsCRP can be used as an important diagnostic tool to exclude and evaluate the severity of preeclampsia.

Key words : pregnancy, preeclampsia, biomarkers, birth weight, high-sensitive C-reactive protein

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Introduction

Preeclampsia (PE) is a pregnancy-specific syndrome that causes reproductive disadvantages unique to human beings[1]. PE isa leading cause of maternal morbidity and mortality due to eclampsia, hemolysis, elevated liver enzymes, low platelet count syndrome (HELLP), central nervous system, and renal and pulmonary complications[2]. PE affects 2–8% of all pregnancies[2, 3], with a recurrence rate of 13–18%[1] in subsequent pregnancies. The disease process in PE progresses in two stages: the placental stage and the inflammatory stage[4, 5]. In the placental stage, an atypical maternal immune response to trophoblasts causes either impaired decidualization or improper uterine preconditioning[4]. Several biomarkers of uteroplacental origin have been widely studied to predict PE, including vascular endothelial growth factor (VEGF), placental growth factor (PGF), and pregnancy-associated plasma protein A (PAPP-A) and many others[6]. However, these tests are expensive and have a lim-

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ited availability in low-resource countries. The second stage is associated with inflammatory changes[4, 5]. Inflammation and endothelial dysfunction are considered crucial in the disease process and are accompanied by elevated levels of serum inflammatory markers, such as C-reactive protein (CRP)[7, 8]. The estimation of high-sensitive CRP (hsCRP) is more sensitive than conventional CRP in inflammatory conditions[9]. A systematic review of 34 studies revealed a positive association between CRP levels and disease onset, especially among healthy individuals with singleton pregnancies with no known risk factors. When measured in the first trimester, CRP levels could be a good indicator to initiate preventive measures[10]. PE is also characterized by hyperuricemia resulting from relative hypovolemia and angiotensin II function, leading to increased tubular reabsorption of urate[11]. Uric acid (UA) may play a role in disease progression because, at higher concentrations, UA inhibits nitric oxide production, leading to poor trophoblast invasion and impaired repair of the endothelial lining[12]. In countries like India, where tertiary centers are overburdened, clinical symptoms of PE are often missed at prenatal clinics, and it is not uncommon for pregnant mothers to attend hospitals for the first time in the late trimesters or not have any prenatal checkups at all. Thus, due to a lack of awareness and compliance, most patients present to healthcare facilities when PE has already developed[13, 14]. Identifying patients with severe diseases is essential to prevent maternal near-misses and deaths.

In this setting, hsCRP can be used for point-of-care testing, and wider applicability of this test is only possible when the predictive value and discriminatory ability of the test are known. Therefore, in this prospective study, our objectives were to compare single-measurement of hsCRP levels in pregnant women (PW) with non-severe PE and severe PE, and in PW with no evidence of PE. Further, our aim was to establish biomarker cutoff levels for the detection of PE and severe PE and to determine the association between hsCRP cutoff levels within PW with low birth weight (LBW) and preterm delivery. We also aimed to compare serum UA levels, a common test for predicting PE, with hsCRP levels.

Patients and Methods

This was an observational prospective study conducted over 18 months from March 2021 to September 2022 at the Department of Obstetrics and Gynaecology of a tertiary care center in Eastern India. The Calcutta National Medical College Institutional Ethics Committee approved the study protocol (approval number: 22/1/2021;G&O).CNMC/100 (1)-2021. This study complied with the revised Helsinki Declaration of Bioethics Policy. All the participants provided informed consent. The anonymity and confidentiality of the data were maintained.

The sample size was calculated to be 185 using the Burderer formula, considering 8% disease prevalence[2], 96% expected sensitivity, and 93% expected specificity for hsCRP at a 95% confidence level and 10% precision[15, 16]. As per available resources, 180 PW were recruited for the study and were divided into three equal groups (n=60 each): control, non-severe PE, and severe PE groups. The control group comprised PW with uncomplicated pregnancies. Participants were selected from among PW attending the Antenatal Outpatient Department (OPD) and the Obstetrics Emergency Department of Obstetrics and Gynecology.

PE was defined by the presence of high blood pressure (BP) (systolic BP >140 mm/Hg or diastolic BP >90 mm/Hg) and proteinuria >0.3 mg/day in PW beyond 20 weeks of gestation[17]. PW with PE were further divided into severe and non-severe groups based on the following characteristics:

Severe PE was defined by one of the following criteria[18]:

- Systolic BP ≥160 mm/Hg
- Diastolic BP ≥110 mm/Hg
- Proteinuria >300 mg (0.3 mg/day or ≥1+ dipstick)
- Presence of headache, upper abdominal pain or epigastric pain, visual disturbance.
- Pulmonary edema
- Oliguria (urinary output ≤400 mL/day)
- Thrombocytopenia (platelets <100,000/day)
- Elevated serum transaminase >2 times the upper limit of the normal range
- Elevated serum creatinine levels
- Intrauterine growth restriction of fetus

PW experiencing PE but not meeting the aforementioned criteria were classified into the non-severe PE group. However, mothers with eclampsia and those with fetal congenital anomalies, intrauterine death, or multifetal pregnancy were excluded from the study. Mothers who refused to provide consent or were aged <18 years were also excluded.

Approximately 5 mL of venous blood was collected during enrolment from study participants under absolute fasting conditions. In addition to routine blood parameters, hsCRP levels were measured using a turbidimetric immunoassay. Fresh serum was used for all assays. HsCRP levels were measured using the Erba diagnostic kit[19]. Serum UA levels were estimated by using the uricase-PAP method[20].

Apart from this urine dipstick test, 24-hurinary protein analysis was performed along with cardiotocography (CTG) and ultrasound examination (USG) for growth scan by color Doppler using Healthcare Logiq P9 model equipped with a 10–13 MHz abdominal transducer to assess fetal well-being. Findings such as oligohydramnios, abnormal Doppler indices, and end-diastolic flow of the umbilical artery were recorded to exclude fetal growth restriction (FGR).

All participants were followed up and their pregnancy outcomes were recorded. Data were collected using a predesigned and formatted case record form and interpreted ac-

cording to standard protocols.

Statistical analysis

Proportions were calculated for categorical variables, and means with standard deviations (SD) were calculated for continuous variables. Group means were compared using analysis of variance (ANOVA) with a post-hoc Tukey's HSD test. Group proportions were compared using the chi-square test. Receiver operating characteristic (ROC) curves were constructed to determine the sensitivity and 1-specificity of hsCRP and UA for the detection of PE and severe PE. The area under the curve (AUC), Youden index, and J-statistics were calculated. All women were dichotomized based on the hsCRP cutoff levels (cutoff levels determined based on ROC curves). The crude odds ratio (COR) or risk for LBW and preterm birth were calculated for the ascertained biomarker cutoff levels. All analyses were performed using the Statistical Package for Social Sciences (SPSS) v.23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA: IBM Corp.).

Results

Sixty PW were recruited for each of the healthy, non-severe, and severe PE groups, for a total of 180 participants. The recruitment was conducted during the third trimester of pregnancy. The groups of PWwere comparable in terms of age, education, parity, abortion history, and hemoglobin levels at recruitment. However, the pre-pregnancy body mass index (BMI) differed between healthy PW and PW with PE groups. A chi-square test of independence showed that the relationship between abnormal USG findings and PE was highly significant, as 83.3% of women in the severe PE group had abnormal USG findings. The biomarkers under study, serum hsCRP, UA, and 24-hurinary protein excretion, differed significantly between the healthy and non-severe PE, non-severe PE and severe PE, and healthy and severe PE groups by Tukey's HSD post hoc test. Gestational age at delivery differed between non-severe and severe PE groups. The birth weights of newborns differed between non-severe and severe PE and between the healthy and severe PE pairs. Emergency LSCS was associated with PE, whereas the proportion of preterm births did not vary between the groups (Table 1).

Women with PE had higher pre-pregnancy BMI. The biomarkers serum hsCRP, UA and 24-hr urinary protein excretion significantly differed between healthy women and women with PE and had higher values under more severe conditions. Women with severe PE were more likely to deliver earlier than those with non-severe PE. The birth weights of the newborns were comparable between non-severe PE and normotensive women.

Figures 1 and 2 show the ROC curves for hsCRP and UA in the detection of PE in normotensive women and to distinguish severe PE from non-severe PE. The AUC showed high values for both biomarkers in both test types, and their ability to detect the condition using a positive test had high statistical significance. Based on the AUC, hsCRP level was

Table 1 Comparison of healthy pregnant women and pregnant women with non-severe or severe preeclampsia

Variables	Healthy (n=60)	Non severe PE (n=60)	Severe PE (n=60)	Differences of mean by ANOVA F (Sig)
	Mean (SD)			
Age	21.9 (3.3)	22.9 (4.2)	21.9 (4.3)	1.2 (0.3)
Pre-pregnancy BMI *	19.8 (3.6)	21.5 (2.3)	22.2 (2.3)	11.6 (<0.001)
Weeks of gestation at delivery*	38.1 (1.3)	38.4 (1.3)	37.6 (1.8)	4.8 (0.009)
Hb%	10.9(1.4)	11.2 (1.3)	10.9 (1.4)	1.0 (0.4)
Uric acid *	4.0 (0.8)	5.2 (1.2)	7.4 (2.1)	85.2 (<0.001)
hsCRP*	1.4 (0.9)	6.2 (2.4)	26.9 (14.2)	158.7 (<0.001)
24-hour urinary protein*	112.0 (39.2)	228.4 (81.1)	348.5 (48.7)	240.0 (<0.001)
Birth weight of newborn in grams*	2,701 (405.7)	2,594.7 (451.0)	2,358.3 (382.7)	10.8 (<0.001)
Proportion with the attribute	Healthy (n=60)	Non severe PE (n=60)	Severe PE (n=60)	Chi-square test of association χ^2 (DF, Sig)
No formal education	48 (80.0)	40 (66.7)	43 (71.7)	2.7 (2, 0.3)
Past abortion	13 (21.7)	10 (16.7)	10 (16.7)	0.7 (2, 0.7)
Nullipara at enrolment	38 (63.3)	40 (66.7)	45 (75.0)	2.9 (4, 0.6)
Abnormal USG*	4 (6.7)	16 (26.7)	50 (83.3)	79.9 (2, P< 0.001)
Preterm births	6 (10.0)	6 (10.0)	14 (23.3)	5.7 (2, 0.06)
Emergency LSCS *	12 (20.0)	28 (46.7)	37 (61.7)	21.8 (2, P<0.001)

*P<0.05. ANOVA: analysis of variance; BMI: body mass index; hsCRP: high-sensitive C-reactive protein; USG: ultrasound examination; LSCS: lower segment Caesarean section; PE: preeclampsia; DF: degree of freedom.

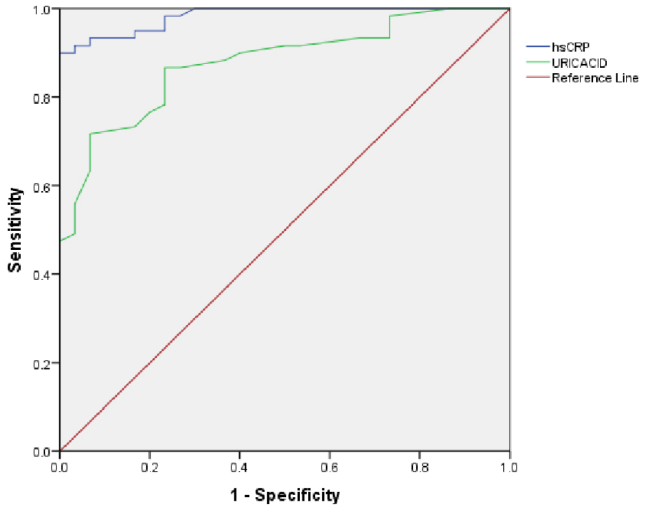

Figure 1 Receiver operating characteristic (ROC) curve of high-sensitive C-reactive protein (hsCRP) and uric acid levels for detection of preeclampsia (n=180)

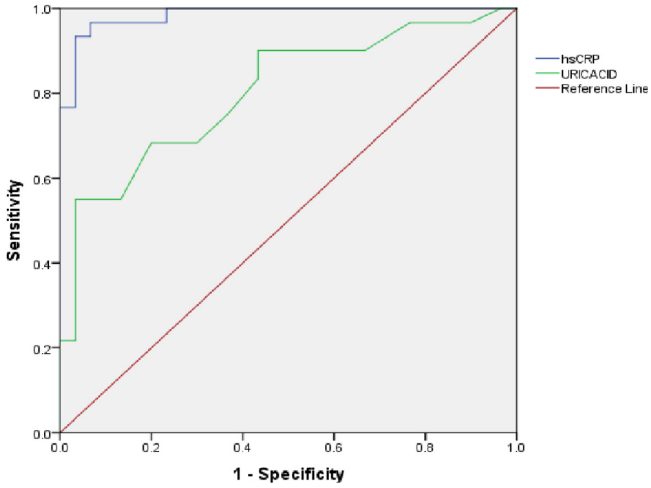

Figure 2 Receiver operating characteristic (ROC) curve of high-sensitive C-reactive protein (hsCRP) and uric acid levels for detection of severe preeclampsia (n=120)

Table 2 Area under curve (AUC) for test types and variables

Test type	Test result variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
					Lower bound	Upper bound
To detect PE	hsCRP	0.983	0.007	0.000	0.970	0.996
n=180	Uric Acid	0.878	0.025	0.000	0.829	0.927
To detect severe PE	hsCRP	0.984	0.008	0.000	0.968	1.000
n=120	Uric Acid	0.803	0.040	0.000	0.725	0.882

[a]Under the nonparametric assumption, [b]Null hypothesis: true area=0.5. hsCRP: high-sensitive C-reactive protein; PE: preeclampsia.

the preferred test (Table 2).

Test cutoffs values were determined based on the highest J-statistic value. The cutoff for hsCRP was 3.72 mg/L to detect PE from normotensive women with 90% sensitivity and 100% specificity and 8.75 mg/L to distinguish severe PE from non-severe PE with 97% sensitivity and 93% specificity. Similar cutoffs for UA were 5.15 mg/dL and 7.00 mg/dL. However, the J-statistic and sensitivity of UA in differentiating non-severe PE from severe PE were low. The UA level cutoff had a high sensitivity of 90% and resulted in low specificity and an even lower J-statistic (Table 3).

As birth weights were significantly lower in the severe PE group, and considering the good performance of hsCRP in detecting both PE and severe PE, the measured cutoffs were tested for association with LBW (birth weight <2,500 g) and preterm delivery. Women with single hsCRP values at a cutoff higher than the PE level had a 2.8 times higher risk of LBW, whereas women with an hsCRP value at a cutoff higher than the severe PE level had 4.1 times higher risk of LBW and 2.6 times higher risk of preterm birth (Table 4).

Discussion

In the present study, hsCRP levels were found to be highly sensitive and specific markers for the detection of PE, with cutoffs set at 3.72 mg/L to detect PE from normotensive women and 8.75 mg/L to detect severe PE. Despite progress in medical management, PE remains a major cause of maternal and perinatal morbidity and mortality worldwide owing to varying degrees of end-organ damage[21, 22]. Endothelial dysfunction, which causes the release of inflammatory markers, may play a key role in disease pathogenesis[23]. Evidence suggests that hsCRP levels can predict the onset of PE when measured during the first half of pregnancy[21, 24]. Antenatal care coverage (ANC) in India is approximately 59%, but varies from 21% to 93% from one region to another[25]. Different measures taken by the government to improve the detection of PE and other high-risk conditions in pregnancy

Table 3 Cutoff levels for high-sensitive C-reactive protein (hsCRP) and uric acid as markers to detect preeclampsia and severe preeclampsia

Test type	Test variable	Cut-off value for positive test	Sensitivity	Specificity	J-statistic (Youden index)
To detect PE	hsCRP	3.72	0.90	1.00	0.90
n=180	Uric Acid	5.15	0.72	0.93	0.65
To detect severe PE	hsCRP	8.75	0.97	0.93	0.90
n=120	Uric Acid (high specificity)	7.00	0.55	0.97	0.52
	Uric Acid (high sensitivity)	5.35	0.90	0.57	0.47

PE: preeclampsia.

Table 4 Association of high-sensitive C-reactive protein (hsCRP) cutoff levels with low birth weight and preterm delivery (n=180)

	hsCRP ≥8.75 n=62 number (%)	hsCRP <8.75 n=118 number (%)	Chi-square test of association χ^2 (DF, Sig)	COR (95% CI)
Low birth weight	40 (64.5)	36 (30.5)	19.3 (1, P<0.001)*	4.1 (2.1–7.9)
Preterm	14 (22.5)	12 (10.2)	5.1 (1, P=0.02) *	2.6 (1.1–5.9)
	hsCRP ≥3.72 n=108	hsCRP <3.72 n=72		
Low birth weight	56 (51.9)	20 (27.8)	10.3 (1, P=0.001) *	2.8 (1.4–5.3)
Preterm	18 (16.7)	8 (11.1)	1.08 (1, P=0.3)	1.6 (0.6–3.9)

*P<0.05, COR: crude odds ratio; hsCRP: high-sensitive C-reactive protein; DF: degree of freedom.

have experienced setbacks due to low ANC coverage, shortage of staff, and overcrowding of public health facilities[26]. Thus, the search remains for low-cost, easy-to-administer, highly sensitive, and specific point-of-care tests to detect PE, which aligns with the broader goal of ending preventable maternal deaths[26]. Our study showed that hsCRP levels were elevated in PW with PE compared to normotensive PW. Endothelial dysfunction along with plasma volume depletion in PW with PE maintains high serum hsCRP levels when compared with healthy individuals[8, 27, 36]. In a similar study by Chen *et al.*, ROC curve analysis showed higher hsCRP values reflected worse conditions[28]. Hwang *et al.* also reported that hsCRP can be used as a marker of disease severity in PW with PE[29]. The cutoff for hsCRP was 9.66 mg/L in the study by Ertas *et al.* to differentiate severe PE from the mild form of the disease, which aligns with the findings of the present study[22].

We found that the birth weight of newborns, ultrasound features, and color Doppler changes suggestive of FGR significantly varied between healthy PW and PW with severe PE and between severe and non-severe PE pairs (P<0.001; Table 1). PE is characterized by deficient trophoblastic invasion, and the placentas of both PW with PE and FGR exhibit a high degree of apoptosis[30, 31]. Such a high apoptotic index in the placenta may stimulate CRP release, which also acts as a scavenger of chromosomal substances released from those apoptotic cells[32]. This can explain the inverse relationship between fetal growth and serum hsCRP levels. We quantified hsCRP levels between PW with PE and those without PE and between PW with severe and non-severe PE and found elevated hsCRP was strongly associated with LBW at 3.72mg/L and 8.75 mg/L or more, respectively. Ertas *et al.* found a similar effect of severe PE on FGR development at 9.66 mg/L a cutoff level or above[22]. We also observed higher rates of preterm delivery in PW with severe PE (P=0.02) when compared with PW with non-severe PE. The number of cesarean deliveries was significantly higher in PW with severe PE than those with non-severe PE and the healthy controls (Table1). According to Wu *et al.*[33], cesarean section rates were significantly higher in the PE group than in the control group (P-value <0.01).

Coppage *et al.* reported a 100% cesarean section rate in pregnancies complicated by severe PE in a trial involving 114 participants[34]. Karinen *et al.* reported a higher rate of elective preterm delivery among women with severe disease than among those with mild PE at term[35]. We found serum UA could also differentiate the PE diseased group from healthy controls at a cutoff level ≥5.15 mg/dL but it failed to show its role as a prognostic marker (Table 3). Previous studies and one systematic review reported that serum UA

estimation does not help predict complications in PE but might predict the latency period from diagnosis to delivery[36–38]. PE is a systemic inflammatory condition; however, due to variations in inflammatory responses, the probable gestational period during which the maximum inflammatory response is reached is not known[22, 39]. Moreover, the maternal inflammatory response is generated in the early weeks of gestation with an influx of macrophages and pro-inflammatory natural killer cells into the decidua during implantation, resulting in an increase in CRP by the fourth week of gestation[24, 40]. Therefore, the role of estimating hsCRP levels in predicting disease onset remains questionable. To our knowledge, this is the first study to determine the role of a single estimation of serum hsCRP at point-of-care as a screening tool to separate PW with PE from healthy PW and to evaluate the severity of PE and its impact on feto-maternal outcomes.

Limitations

Our study had some limitations. First, this was a single-site study with a small sample size; hence, the possibility of confounding with pre-existing unknown inflammatory conditions cannot be ignored. No particular gestational age was chosen, and a single hsCRP estimation was performed with no follow-up in the postnatal period. Moreover, randomized controlled trials are required to study the roles of anti-inflammatory agents, antioxidant drugs, and disease outcomes.

Conclusions

HsCRP can be used as an easily accessible, highly sensitive, and specific screening tool among PW with PE to identify those who might develop severe complications. HsCRP has an important role to provide rapid point-of-care testing in Low Middle Income Countries (LMIC)s where maternal health is often compromised due to poor utilization of regular antenatal care. Additionally, BP measurement is subject to human and instrumental error; thus, biomarker testing can be a useful complementary assessment. The potential for incurring increasedcosts is likely to be balanced by early detection of PE, rapid bed turnover, less Neonatal Intensive Care Unit (NICU) admissions and reduced treatment costs for PE complications. Further health economics research is necessary to integrate hsCRP testing into maternal healthcare programs. Further research is needed to determine the optimum time for testing, the impact of single versus serial testing, and the correlation between specific clinical signs with hsCRP levels.

Conflict of interest: None.

Funding information: None.

Ethics approval and consent to participate: The study protocol received prior approval from the Calcutta National Medical College Institutional Ethics Committee (approval number: 22/1/2021, G&O).CNMC/100 (1)-2021. Informed consent was obtained from each participants after full disclosure of the aims and procedures of the study.

Consent for publication: All the authors have accepted responsibility for the entire manuscript content, approved its submission, and provided consent for publication.

Data availability statement: The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Author contributions: JB, DM: Concept, study design. MD, KK: Data entry and analysis. LJ, AM: Literature Review. SD: Final editing of draft

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