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ORIGINAL ARTICLE

Prediction of Adverse Maternal Outcomes in Preeclampsia Using a Risk Prediction Model

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About the Author

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Abstract

Background This study was conducted to evaluate how the preeclampsia integrated estimate of risk (fullPIERS) model performs in the prediction of adverse maternal outcomes when the predictor variables are all obtained within 24-h of admission for preeclampsia.

Methods A prospective cohort study on 323 women who fulfilled definite inclusion and exclusion criteria was conducted. Subjects were monitored for clinical symptoms of preeclampsia, biochemical parameters, and adverse maternal and neonatal outcomes. A risk prediction score was calculated using the fullPIERS calculator. Statistical analysis of rates and ratios was carried out by assessing χ^2 test and odds ratio.

Results 18.3 % ($n = 60$) had adverse maternal outcome and 42.8 % ($n = 138$) had adverse fetal outcome, and 43 (13.35 %) had combined adverse maternal and perinatal outcome. Dyspnea, visual disturbances, epigastric pain, and Sp_{O_2} appeared to be highly significant risk factors. In the biochemical variables studied, serum creatinine and serum uric acid were found to have a significant association. The association between adverse perinatal outcome and vaginal delivery was highly significant (OR 0.35, 95 % CI 0.19, 0.63), and the P value was 0.0005. The likelihood ratio associated with the highest risk group (predicted probability of the outcome ≥30 %) showed excellent performance (i.e., 17.5) of fullPIERS model as a rule in test.

Shruti Agrawal is a Third-Year Resident; Nandita Maitra is a Professor and Head.

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Conclusion The fullPIERS model performed well in the prediction of adverse maternal outcomes in women with preeclampsia. It is easy to use. The model is based on the use of few important clinical and biochemical parameters and does not require extensive laboratory testing. Although it might be of limited use in a well-equipped tertiary care facility, this model can be utilized in the setting of district or sub-district level hospitals to identify patients who are at risk of complications due to preeclampsia. Timely referral to a higher center will help in reducing the morbidity and mortality associated with this condition.

Keywords Risk prediction · Preeclampsia · Maternal outcomes

Introduction

Preeclampsia and the other hypertensive disorders of pregnancy (HDPs) remain leading causes of maternal and perinatal morbidity and mortality; the World Health Organization estimates that at least one woman dies every 7 min from the complications of HDPs [1].

While preeclampsia has the potential for serious complications, most cases of preeclampsia are mild and require minimal clinical treatment. Management of preeclampsia may include increased maternal and fetal surveillance, blood pressure control, and seizure prophylaxis, but ultimately delivery of the infant is the only definitive treatment [2].

There have been limited studies examining the role of maternal symptoms in predicting outcomes. Menzies et al. [3] have stated that the preeclampsia severity criteria identified by both the Canadian Hypertension Society and the National High Blood Pressure Education Program were not predictive of maternal or perinatal morbidity. Current guidelines that make use of these severity criteria, such as those written by the Society of Obstetricians and Gynecologists of Canada [4] and the American College of Obstetricians and Gynecologists [5], for evaluating the severity of preeclampsia are not uniform and have not been proven effective.

The decision for preterm delivery of the fetus in the setting of preterm preeclampsia (at 34 weeks' gestation) is based on the estimated risk of an adverse outcome balanced with the considerable benefit to the fetus if pregnancy is prolonged. Expectant management is usually attempted in women thought to be at high risk for complications until 34 weeks' gestation, after which the neonatal outcomes are excellent and the benefit for the fetus is usually outweighed by the estimated risk to the mother [5].

The preeclampsia integrated estimate of risk (fullPIERS) model is a recently developed tool for predicting adverse maternal outcomes following the diagnosis of preeclampsia within 48-h after admission to the hospital. This tool helps to determine the maternal risks in the setting of preeclampsia and to decide for triage, transport, and treatment along with assessment of neonatal risk based on gestational age at presentation [6]. The goal of the PIERS model was to develop and validate an outcome prediction tool that identifies which hospitalized women with preeclampsia will suffer adverse maternal or perinatal outcome.

This study was conducted to evaluate how the fullPIERS model performs in the prediction of adverse maternal outcomes when the predictor variables are all obtained within 24-h of admission for preeclampsia.

Materials and Methods

This was a prospective cohort study on 323 women who fulfilled the following inclusion and exclusion criteria.

Inclusion Criteria

(1) Hypertension (systolic blood pressure of 140 mmHg or greater and/or diastolic blood pressure of 90 mmHg or greater, taken twice more than 4 h apart) after 20 weeks of gestation.
(2) Proteinuria defined as 0.3 g/dl or more or 2+ or more dipstick proteinuria after 20 weeks of gestation
(3) Non-hypertensive and non-proteinuria HELLP syndrome, using Sibai's criteria [7].
(4) An isolated eclamptic seizure without preceding hypertension with or without hypertension and proteinuria.

Exclusion Criteria

- Women were excluded from the cohort if they were admitted to the hospital in spontaneous labor or if any element of combined adverse maternal outcome occurred prior to their meeting the eligibility criteria or before the collection of predictor variables was possible.

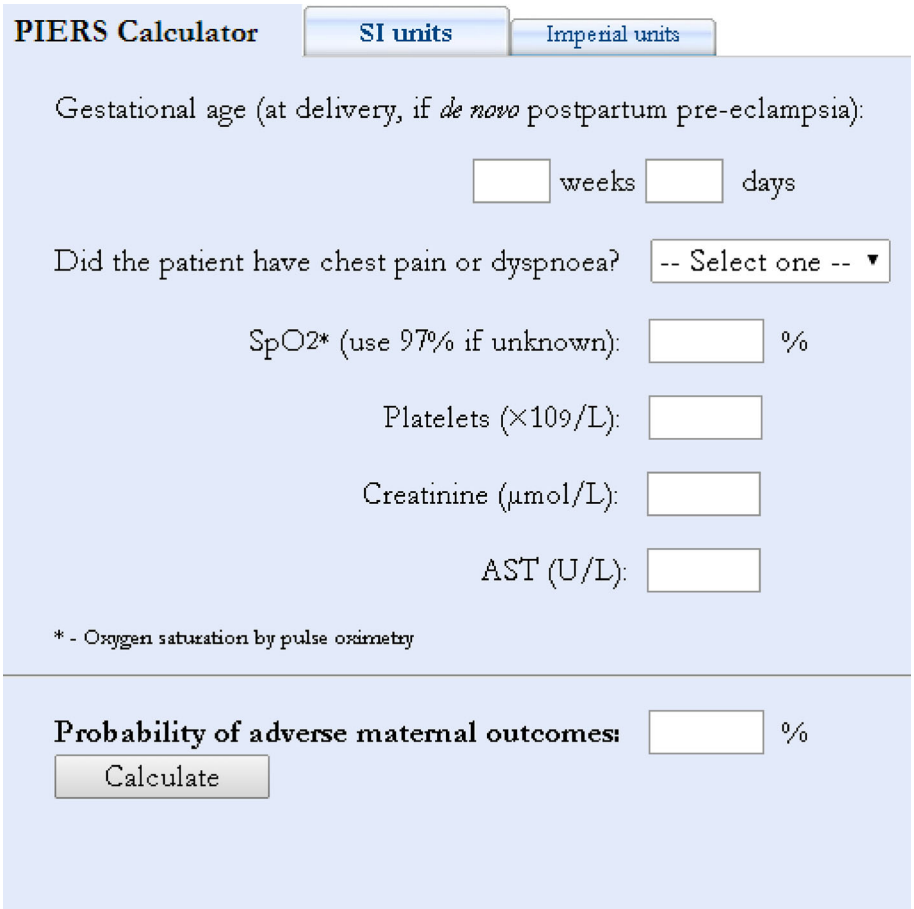
Monitoring and Investigations

In addition to measurement of maternal blood pressure, the following investigations were performed within the first 24-h of admission.

(1) *Hematology* full blood screen, international normalized ratio, APTT, and fibrinogen.

(2) *Renal* urea, creatinine, electrolytes, uric acid, and dipstick. While other testing occurred twice weekly, urine was also assessed after 24-h of collection for protein and creatinine clearance (on admission and once weekly thereafter).
(3) *Hepatic* aspartate transaminase, alanine transaminase. LDH, bilirubin, albumin (plasma,) and random glucose.
(4) *Respiratory* pulse oximetry.

myocardial ischaemia or infarction; acute renal insufficiency or failure; dialysis; pulmonary oedema; Sp_{O_2} <90 %; requirement of >50 % fractional inspired oxygen (Fi_{O_2}) for more than 1 h; intubation (other than solely for cesarean section); transfusion of any blood product; severe thrombocytopenia (<50 × 109/l) in the absence of blood transfusion; and placental abruption. A combined risk was then calculated using the PIERS calculator (http://piers.cfri.ca/PIERSCalculatorH.aspx) [8].



(5) *Fetal surveillance* (*antenatal only*) cardiotocography daily, ultrasound for assessment of fetal weight (every 14 days,) and amniotic fluid volume and umbilical artery Doppler (twice weekly).

The combined maternal adverse outcome included maternal mortality and any of the following maternal morbidity: hepatic dysfunction, haematoma, or rupture; one or more seizures of eclampsia; Glasgow coma score <13; stroke; reversible ischaemic neurological deficit; transient ischaemic attack; posterior reversible encephalopathy syndrome; cortical blindness or retinal detachment; need for positive inotrope support; infusion of a third parenteral antihypertensive;

Perinatal Outcomes

The perinatal outcomes include perinatal or infant mortality, bronchopulmonary dysplasia, necrotizing enterocolitis, grade III or IV intraventricular hemorrhage, cystic periventricular leukomalacia, or stages 3–5 retinopathy of prematurity.

Predictor variables were collected within 24-h of hospital admission. Statistical analysis of rates and ratios was carried out by assessing χ^2 test and odds ratio. Significance was set at $P < 0.05$. Univariate Logistic regression was done using the SPSS software version 17. Sensitivity,

specificity, and positive likelihood ratios (LRs) were calculated using MedCalc software.

Results

Three hundred and twenty-three women were recruited based on a sample size calculation. One woman was lost to follow-up. So the outcome was studied in 322 subjects (Table 1).

- There was no difference in the mean ± SD values for maternal age in years between the two groups; however, the mean ± SD values for gestational age at presentation and delivery; and systolic, diastolic, and mean blood pressure were highly significant. Among the 323 subjects, 157 (48.6 %) were primigravida of which 27 (17.1 %) had adverse maternal outcome and 129 (82.1 %) did not. One hundred and sixty-six (51.3 %) subjects were multigravida among which 33 (19.8 %) developed adverse outcome and 133 (80.1 %) had no adverse outcome. All subjects had singleton pregnancy. Two hundred and twenty-five (69.6 %) subjects required two antihypertensives, whereas 98 (30.3 %) subjects required only one antihypertensive. Thirty-seven subjects were given prophylactic $MgSO_4$, and 33 subjects required therapeutic $MgSO_4$. Parity had no significant association with adverse maternal outcome. The prophylactic dose of magnesium sulfate was the same as the therapeutic dose as given under the Pritchard regime; that a loading dose of 14 g (10 g intramuscular injection and 4 g intravenously) followed by 5 g intramuscularly every 4 h continued till 24-h post partum. Thirty-seven subjects received prophylactic magsulf. Out of these 37 subjects, 10 (27.0 %) had an adverse maternal outcome. Table 2 shows the maternal symptoms and biochemical parameters in relation to adverse maternal outcomes. Sixty subjects of 322 had an adverse maternal event. There was no maternal mortality in the study group. Two subjects who had an adverse outcome did not have any of the symptoms listed above. All biochemical parameters studied were found to have a strong association with adverse maternal outcome. Serum creatinine >1.1 mg/dl [OR 8.9 (4.8–16.5)] and serum uric acid >6 mg/dl [OR 8.14 (4.2–15.57)] had the highest association. When univariate logistic regression was applied to significant variables, only serum creatinine and serum uric acid were found to be highly significant with independent association.

There were 139/322 (43.16 %) adverse perinatal events reported. Among the symptoms, visual disturbances [OR 7.4 (2.77–20.11)] were more strongly associated with an adverse perinatal outcome. Among the biochemical markers, AST, serum creatinine, and serum uric acid did not show any significant association. Dipstick proteinuria 2+ or more had a significant association [OR 3.8 (2.2–6.4)].

Forty-three (13.35 %) subjects had combined maternal and perinatal adverse outcomes. All symptoms and biochemical markers were found to show a statistically significant association with the combined outcome (Table 3).

One hundred and thirty-nine (43.16 %) subjects had spontaneous vaginal delivery, 122 (38.8 %) delivered after successful induction of labor, and 58 (18.01 %) required cesarean delivery. The association between vaginal mode of delivery and adverse maternal outcome was not statistically significant (OR 0.57, 95 % CI 0.29–1.12). The

Table 1 Baseline characteristics of subjects

Characteristics	With outcome	Without outcome	*P* value
Mean age in years (SD)	24.8 ± 2.9	24.7 ± 3.9	0.9
Mean period of gestation in weeks (SD)	35.47 ± 3.55	34.5 ± 4.5	0.01
Mean gestational age at delivery ±SD	34.4 ± 4.2	35.7 ± 3.3	0.01
Mean systolic blood pressure (at the time of admission) mmHg	167.6 ± 18.8	156.6 ± 15.3	0.0001
Diastolic blood pressure (at the time of admission) mmHg	102.69 ± 8.1	98.02 ± 9.1	0.0001
Mean arterial blood pressure (mmHg)	118.64 ± 10.3	115.01 ± 11.2	0.022
Primigravida ($n = 157$)	27 (17.1 %)	129 (82.1 %)	0.55 (0.48–1.48)
Gravida 2 or more ($n = 166$)	33 (19.8 %)	133 (80.1 %)	
Singleton pregnancy ($n = 322$)	60 (18.6 %)	262 (81.3 %)	NA
No. of subjects requiring one antihypertensive ($n = 98$)	5 (5.1 %)	93 (94.8 %)	
No. of subjects requiring two antihypertensives ($n = 225$)	55 (24.4 %)	170 (75.5 %)	
No. of subjects requiring prophylactic magnesium sulfate ($n = 37$)	10 (27.7 %)	27 (72.9 %)	
No. of subjects requiring therapeutic magnesium sulfate ($n = 33$)	33 (100)	0	

Table 2 Maternal symptoms, biochemical markers, and adverse maternal outcome

	Adverse maternal outcome Present *n* (%) ($n = 60$)	Adverse maternal outcome Absent *n* (%) ($n = 262$)	OR (95 % CI)	*P* value
Symptoms				
Headache ($n = 62$)	17 (27.41)	45 (72.58)	1.91 (1.003–3.65)	0.0489
Visual disturbances ($n = 29$)	11 (37.93)	18 (62.06)	3.05 (1.35–6.82)	0.006
Right upper quadrant or epigastric pain ($n = 38$)	12 (31.57)	26 (68.42)	2.27 (1.07–4.82)	0.03
Chest pain or dyspnea ($n = 40$)	18 (45.0)	22 (54.0)	4.69 (2.32–9.49)	<0.0001
Biochemical markers				
Platelet count (<1.5 lacs) ($n = 80$)	23 (28.75)	57 (71.25)	2.2 (1.23–4.06)	0.0083
AST (>40 U/l) ($n = 122$)	31 (25.40)	91 (74.6)	2.0 (1.13–3.54)	0.015
Serum creatinine (>1.1 mg/dl) ($n = 77$)	37 (48.05)	40 (51.2)	8.9 (4.8–16.5)	<0.0001
Serum uric acid (>6 mg/dl) ($n = 56$)	29 (51.8)	27 (48.21)	8.14 (4.2–15.57)	<0.0001
Dipstick proteinuria (≥2) ($n = 87$)	30 (34.48)	57 (65.51)	3.59 (2.0–6.4)	<0.0001

Table 3 Maternal symptoms, biochemical markers, and adverse perinatal outcome

Symptoms	Adverse perinatal outcome Present ($n = 139$)	Adverse perinatal outcome Absent ($n = 184$)	OR (95 % CI)	*P* value
Headache ($n = 62$)	40 (64.51)	22 (35.48)	2.97 (1.67–5.29)	0.002
Visual disturbances ($n = 29$)	24 (82.75)	5 (17.24)	7.4 (2.77–20.11)	0.0001
Right upper quadrant or epigastric pain ($n = 38$)	28 (73.68)	10 (26.31)	4.3 (2.05–9.38)	0.0001
Chest pain or dyspnea ($n = 40$)	25 (62.5)	15 (37.5)	2.47 (1.24–4.89)	0.009
Biochemical markers	Adverse fetal outcome Present *n* (%)	Adverse fetal outcome Absent *n* (%)	OR (95 % CI)	*P* value
Platelet count (<1.5 lacs) ($n = 80$)	44 (55.0)	36 (45)	1.89 (1.13–3.15)	0.014
AST (>40 U/l) ($n = 122$)	58 (47.54)	64 (52.45)	1.33 (0.84–2.09)	0.21
Serum creatinine (>1.1 mg/dl) ($n = 77$)	43 (55.84)	34 (44.15)	1.96 (1.1–3.29)	0.01
Serum uric acid (>6 mg/dl) ($n = 56$)	29 (51.78)	27 (48.21)	1.5 (0.85–2.7)	0.15
Dipstick proteinuria (≥2)	58	29	3.8 (2.2–6.4)	<0.0001

association between adverse perinatal outcome and vaginal delivery was highly significant (OR 0.35, 95 % CI 0.19, 0.63) and *P* value was 0.0005. Thus, vaginal delivery, either spontaneous or induced, was better for both mother and fetus (Table 4).

Table 5 has been derived after calculating the probability of risk using PIERS calculator. For all subjects in the study, performance of the fullPIERS model was assessed by limiting predictor variable data to the available values of the markers within 24-h of admission. Using this model to calculate and stratify the probability, we found a positive LR varying from 3.22 (95 % CI 2.4, 4.2) at the lowest cutoff threshold to a positive LR of 17.53 at the highest >30 % (95 % CI 8.52, 36.1) probability cutoff.

Discussion

This study was undertaken to assess the ability of the fullPIERS model to predict adverse maternal outcomes when using only clinical predictor variables available within 24-h of admission. Out of the 322 subjects studied, 18.3 % ($n = 60$) had adverse maternal outcome and 42.8 % ($n = 138$) had adverse fetal outcome, and 43 (13.35 %) had combined adverse maternal and perinatal outcome; 33 subjects (10.24 %) had eclampsia, 13 (4.03 %) had abruptio placentae, 12 (3.7 %) had thrombocytopenia, 8 (2.4 %) subjects developed acute renal failure, 4 (1.24 %) developed HELLP syndrome, 2 (0.62 %) subjects each had pulmonary edema and post

Table 4 Mode of delivery and adverse fetal outcome

Mode of delivery	Adverse fetal outcome Present *n* (%)	Adverse fetal outcome Absent *n* (%)	OR (95 % CI)	*P* value
Vaginal spontaneous ($n = 139$)	27 (19.42)	112 (80.57)	0.35 (0.19–0.63)	0.0005
Vaginal induced ($n = 125$)	74 (59.2)	51 (40.8)		
Cesarean section ($n = 58$)	37 (63.79)	21 (36.2)		

Table 5 Risk stratification, assessing the value of the fullPIERS model in risk prediction, by predicted probability of adverse maternal outcome

Predicted probability (%)	Number of women	Number of women with outcome	% of women with outcome (95 % CI)	Sensitivity (%)	Specificity (%)	Likelihood ratio	95 % CI
0.00–0.99	223	18	8.07	70.0	78.2	3.22	2.4–4.2
1.0–2.4	23	6	26.08	60.0	84.7	3.9	2.7–5.59
2.5–4.9	17	7	41.1	48.3	88.54	4.2	2.7–6.4
5.0–9.9	15	5	33.33	40.0	92.36	5.2	3.11–8.8
10.0–19.9	12	6	50	30.0	94.6	5.6	2.9–10.6
20.0–29.9	5	3	60	25.0	95.4	5.4	2.7–11.05
≥30	27	15	55.5	52.5	97.0	17.53	8.52–36.1
Total	322	60	18.6				

partum hemorrhage, and 2 (0.62 %) developed cortical blindness. One (0.3 %) subject required intubation. There was no maternal mortality.

Dyspnea, visual disturbances, epigastric pain, and Sp_{O_2} that appeared to be highly significant risk factors for prediction of adverse maternal outcomes were not found to be independent risk factors when logistic regression was applied; only headache was associated significantly.

In a systematic review of maternal symptoms in predicting preeclampsia, Thangaratinam et al. found that 6 primary articles with 2573 women were included. The sensitivity and specificity of the symptoms in predicting adverse maternal outcomes were, respectively, as follows: headache 0.54 (95 % CI 0.27–0.79) and 0.59 (95 % CI 0.38–0.76), epigastric pain 0.34 (95 % CI 0.22–0.5) and 0.83 (95 % CI 0.76–0.89), visual disturbances 0.27 (95 % CI 0.07–0.65) and 0.81 (95 % CI 0.71, 0.88), and nausea and vomiting 0.24 (95 % CI 0.21, 0.27) and 0.87 (95 % CI 0.85, 0.89) [9].

Yen et al. in an analysis of the PIERS data reported that of 2023 women who underwent assessment, 52 % experienced at least one preeclampsia symptom, with 5.2 and 5.3 %, respectively, experiencing an adverse maternal or perinatal outcome. No single symptom was found to be a good predictor of adverse perinatal outcomes [10].

Kozic et al. in a subanalysis of the PIERS dataset found that of the 2008 women, 1056 (53 %) had at least one abnormal liver function test result. The odds of having an adverse maternal outcome were higher in women with any abnormal liver function test than in women with normal results [11].

A systematic review on uric acid and preeclampsia found that, in women with preeclampsia, a positive test result of uric acid greater than or equal to a 350-mmol/l threshold predicted eclampsia with a pooled LR of 2.1 (95 % CI 1.4–3.5), while a negative test result had a pooled LR of 0.38 (95 % CI 0.18–0.81). The review concluded that serum uric acid is a poor predictor of maternal and fetal complications in women with preeclampsia [12]. However, Hawkins et al. in a later study concluded that the risk of adverse maternal outcome (OR 2.0; 95 % CI 1.6–2.4) and adverse fetal outcome (OR 1.8; 95 % CI 1.5–2.1) increased with increasing concentration of uric acid [13]. Our study found uric acid and creatinine to be independent predictors of both adverse maternal and fetal outcomes.

In an analysis of the PIERS dataset, Beth Payne et al. concluded that dipstick proteinuria performs equally well as other methods in assessing proteinuria for the prediction of adverse events. In this study, the level of proteinuria failed to predict adverse pregnancy outcomes [14]. Thangaratinam et al. in a systematic review concluded that all 10 studies predicting maternal outcomes showed that proteinuria is a poor predictor of maternal complications in women with preeclampsia [7].

Regarding mode of delivery in preeclampsia, other studies have found that spontaneous or induced labor has better maternal and neonatal outcomes as compared to

cesarean delivery [15–17]. This is similar to the observations of our study.

The risk prediction model used here showed that the LR associated with the highest risk group (predicted probability of the outcome ≥30 %) showed excellent performance (i.e., 17.5) of fullPIERS model as a rule in test. That is if the fullPIERS model predicted probability is ≥30 %, clinicians can be confident enough that the women is at high risk of an adverse maternal outcome and should adjust their management accordingly. Unlike in the PIERS trial, we have not used the combined adverse maternal outcome but individual outcomes. Secondly, we have used only the second (i.e., 24-h) time frame unlike in the original study which has used the 6- and 24-h time frame. There are limitations inherent to the fullPIERS model—it does not include fetal parameters such as intrauterine growth restriction or fetal death which have been found to be independent risks and only maternal outcomes are assessed.

According to the authors of the fullPIERS study [6], among the 1935 women for whom complete data were available, 65 % of women were stratified as low-risk, with a predicted probability of adverse outcome below 0.025, and at the other end of the risk spectrum were the 4 % at highest risk, with a predicted probability of 0.30 or greater. Only 1 % of women in the low-risk category experienced an adverse outcome, compared with 59 % of those in the high-risk category. The fullPIERS model also was fairly accurate in predicting adverse outcomes occurring later than the first 48-h, for days 2–7 after enrolment. The authors also suggested that some tests can be abandoned, such as routine coagulation studies, and that liver function could be monitored by aspartate aminotransferase alone; once proteinuria has been identified, serum creatinine should be adequate for monitoring renal function. The authors propose that gestational age, maternal symptoms, pulse oximetry, serum creatinine, platelet count, and aspartate transaminase be used to stratify maternal risk during the assessment and surveillance using the fullPIERS equation.

- To conclude, we found that the fullPIERS model performed well in the prediction of adverse maternal outcomes in women with preeclampsia. It is easy to use. The model is based on the use of few important clinical and biochemical parameters and does not require extensive laboratory testing. Although it might be of limited use in a well-equipped tertiary care facility, it may be used for identification and referral of at-risk women to a higher medical facility. This model can be utilized in the setting of district or sub-district level hospitals to identify patients who are at risk of complications due to preeclampsia. Timely referral to a higher center will help in reducing the morbidity and mortality associated with this condition.

Compliance with Ethical Standards

Conflict of interest Dr. Shruti Agrawal has no conflict of interest, and Dr. Nandita Maitra has no conflict of interest.

Informed Consent Disclosure All procedures followed were in accordance with the ethical standards of the Responsible Committee on Human Experimentation (Institutional and National) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

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