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Role of C-Reactive Proteins at Early Gestational Age in Predicting Pre-Eclampsia in Pregnant Females

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ABSTRACT

Background: Pre-eclampsia remains a significant concern in obstetrics due to its potential complications for both mother and fetus. Early detection of pre-eclampsia (PE0 is crucial for timely intervention and management. C-Reactive Protein (CRP), an inflammatory marker, has shown promise as a potential predictor of pre-eclampsia when assessed during early gestational age. **Objective:** To evaluate the diagnostic accuracy of raised serum CRP levels in early gestation to predict the risk of pre-eclampsia in pregnant females. **Study Design:** Prospective validation Study. **Settings:** Outdoor Department of obstetrics and gynecology, Lady Atchison Hospital Lahore. **Duration:** 02-September 2021 to 01-March-2022. **Methods:** A total of 130 pregnant females having gestational age 16 to 20 weeks and presenting in the hospital for regular antenatal visits were included. A five ml venous blood sample was drawn and was sent to the central hospital laboratory for determination of CRP levels from each case. Patients having CRP ≥5.0 mg/L were labelled as high risk of pre-eclampsia. All patients followed till delivery to determine the development of pre-eclampsia. **Results:** The mean age of the patients was found to be 28.16±4.74 years, with a mean BMI of 26.27±5.05 kg/m^2. Among the 130 patients, 12 (9.23%) were identified as having elevated CRP levels, while the remaining 118 (90.77%) showed normal CRP levels. Additionally, pre-eclampsia was diagnosed in 11 (8.46%) of the patients. Evaluation of the diagnostic accuracy of CRP levels revealed a sensitivity of 81.8% and specificity of 97.5%. The positive predictive value (PPV) was calculated at 75%, while the negative predictive value (NPV) stood at 98.3%. **Conclusion:** The study observed that elevated CRP levels in early pregnancy serve as a significant predictor of pre-eclampsia, with sensitivity of 81.8%, indicating its ability to correctly identify those with pre-eclampsia, while the specificity was 97.5%, suggesting its accuracy in ruling out those without the condition.

Keywords: *C-reactive proteins, CRP, Pre-eclampsia, Predictor.*

INTRODUCTION

Preeclampsia (PE) is a condition during pregnancy characterized by hypertension, typically manifesting in around 4-5% of pregnancies.[1] It is characterized by elevated blood pressure and the presence of proteinuria after 20 weeks of gestation.[1] It is one of the main factors contributing to increased morbidity and mortality for both the mother and the fetus. PE cases are increasing globally, with a higher prevalence observed in developing nations compared to developed countries.[2] According to the WHO, the occurrence of preeclampsia ranges from 2% to 10% of pregnancies worldwide. Developing countries report a higher incidence, ranging from 1.8% to 16.7%, while developed countries have a lower rate of 0.4%.[2,3] Pakistan, as a developing nation, experiences a significant burden of preeclampsia cases, with rates as high as 5% among pregnant women.[2,4] The precise cause of pre-eclampsia remains a topic of debate, with numerous factors thought to contribute to its development. Efforts to elucidate the underlying cause have generated a range of hypotheses, yet a singular explanation for the disease is unlikely. Currently, the

most prominent theories focus on inadequate placental development, genetic susceptibility, compromised immune tolerance, systemic inflammation, imbalanced angiogenesis, and insufficient nutritional status.[5,6] However, inflammation and anti-angiogenesis mechanisms have been shown to be crucial elements in its development.[7]

C-reactive protein (CRP) is primarily produced by hepatocytes in reactions to infections and damage to the tissues, and it functions as a sensitive biomarker of inflammation throughout the body. The secretion of proinflammatory cytokines including interleukin-1, interleukin-6, and the alpha form of tumor necrosis factor causes the body to produce CRP.[8] However, it has been indicated that heightened levels of CRP throughout pregnancy are associated with negative pregnancy outcomes.[8,9] Although the elevated levels of maternal CRP have proven effective in identifying infection in cases of preterm labor and premature membrane rupture during pregnancy. Several studies have demonstrated a correlation between systolic and diastolic blood pressure and CRP levels, with higher concentrations associated with the severity of preeclampsia. A recent study by Sharmin *et al* on the accuracy of CRP levels in predicting preeclampsia in pregnant females reported that at cut-off value 5 mg/L is 68.0% sensitive and 98.0% specific for predicting the development of pre-eclampsia. The authors reported preeclampsia in 50 (33.3%) out of 150 patients who were screened for CRP levels.[10] While a study by Gharib M *et al*[1] reported the sensitivity of 100% and specificity as 93.3%.

The aim of the present study was to determine the diagnostic accuracy of CRP levels in predicting the risk of pre-eclampsia in pregnant females. As pre-eclampsia (PE) is a major contributing factor of feto-maternal morbidity and mortality and its diagnosis is often delayed because of the fewer antenatal visits in pregnancy in our population. Because CRP is inexpensive and simple to assess in a laboratory if it is found to have good sensitivity and specificity for predicting pre-eclampsia, then it can be used using an indicator to track or forecast the PE during prenatal treatment. Individuals with elevated CRP may benefit from intensive surveillance, which might be helpful in the PE diagnosis at earliest stages and the timely diagnosis will help to manage pre-eclampsia in a better way and to stop its progression to eclampsia.

METHODS

This prospective validation study was at outdoor Department of obstetrics and gynecology, Lady Atchison Hospital Lahore. Study was done from September 2021 to March-2022. The sample size of 130 patients was calculated by taking estimated frequency of pre-eclampsia in patients with abnormal CRP levels 33.3%,[10] Expected sensitivity of 79.4%, and 71.0% Specificity.[11] And taking 12.5% margin of error. Non-probability consecutive sampling technique was used. All primiparous pregnant females having duration of pregnant 16-20 weeks (on LMP), with singleton pregnancy, aged 18-40 years and those who were presenting for regular antenatal visits were included. Patients presenting with co-morbidities such as gestational diabetes mellitus, renal impairment and patients with evidence of active infections at the time of inclusion in study such as those having fever were excluded. Study was done following approval from hospital ERC and REU of CPSP. Informed consent was taken from the patients. After inclusion in study, venous blood samples were drawn and were sent to the central hospital laboratory for determination of CRP levels. Patients having CRP ≥5.0 mg/L were labelled as high risk of pre-eclampsia. Diagnosis of pre-eclampsia was made according to the criteria as having blood pressure 140/ 90 mm of Hg or more taken on two occasions, 6 hours apart and proteinuria on after the gestational age of 20 weeks in a previously normotensive woman. All patients followed till delivery to determine the development of pre-eclampsia. All the study relevant information was noted on a pre-designed Proforma. All patients who developed pre-eclampsia were managed efficiently as per standard guidelines. Data was entered and analyzed using SPSS version 20.0. Mean and standard deviation was used for quantitative variable such as age, height, weight and BMI. Qualitative variables like pre-eclampsia on CRP and on follow-up were presented as frequency and percentage. 2×2 contingency table was formulated to determine the sensitivity, specificity, PPV and NPV of CRP in predicting pre-eclampsia. Effect modifiers such as age and BMI were controlled through stratification. Data analysis was carried out by using SPSS version 20.

RESULTS

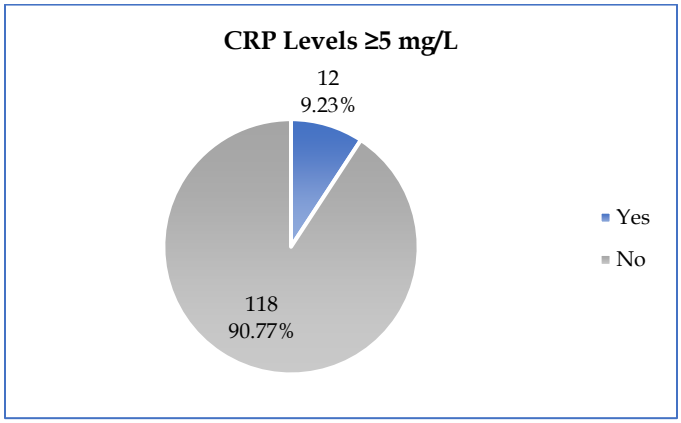
A total of 130 patients were studied with mean age of patients was 28.16±4.74 years, minimum age was 18 years and maximum age was 40 years. Mean Height of patients was 153.7±8.79 cm and mean weight was 61.88±12.12 Kg. Mean BMI of patients was 26.27±5.05 Kg/m^2. Table.1

Table 1: Descriptive statistics of age and Body Mass Index (BMI) n=130

	Age (years)	Height (cm)	Weight (Kg)	BMI (Kg/m^2)
Mean	28.16	153.7	61.88	26.27
S.D.	4.74	8.79	12.12	5.05
Minimum	18	139	45	19.05
Maximum	40	190	92	35.60

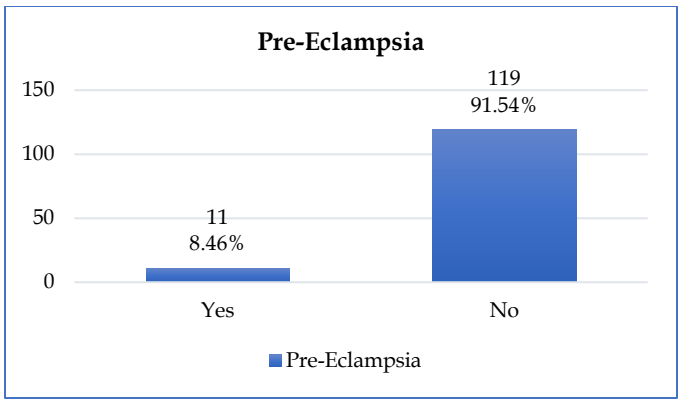
Out of 130, 12 (9.23%) patients were having elevated CRP levels while remaining 118 (90.77%) were having normal CRP levels. Figure 1

Figure 1: Frequency of elevated CRP levels (n=130)



Pre-eclampsia was diagnosed in 11 (8.46%) patients. Fig:2

Figure 2: Frequency of Pre-eclampsia (n=130)



On diagnostic accuracy of CRP levels, CRP levels were 81.8% sensitive 97.5% specific, with PPV of 75% and NPV 98.3%. Table 2

Table 2: Diagnostic Accuracy of CRP Levels in Predicting Pre-eclampsia n=130

Elevated CRP Levels	Pre-eclampsia		Total
	Yes	No	
Yes	09	03	12
No	02	116	118
Total	11	119	130

Sensitivity= 81.8%, Specificity =97.5%, PPV =75% and NPV 98.3%

In terms of the diagnostic accuracy of C-reactive protein (CRP) levels in relation to age groups and body mass index (BMI) among 130 participants. Among those aged 18-29 years, 5.4% had CRP levels > 5 mg/l, while 94.6% had levels less than 5 mg/l. In the 30-40 age group, 14.3% had CRP levels > 5 mg/l, and 85.7% had levels below 5 mg/l. For participants with a BMI less than 24.99 kg/m2, 2.0% had CRP levels > 5 mg/l, while 98.0% had levels below 5 mg/l. Conversely, for those with a BMI of 25.0 kg/m2 or higher, 28.1% had CRP levels above 5 mg/l, and 71.9% had levels below 5 mg/l. Statistical significance was observed in all comparisons ($p < 0.001$) except for BMI (≥25.0 Kg/m2), where the p-value was 0.115. Table.3

Table 3: Diagnostic accuracy of CRP Levels ≥5 mg/L according age groups and BMI n=130

Variables	Pre-eclampsia		Total	p-value
	Yes	No		
Age group (18-29 years)	3	1	4	0.001
	4.1%	1.4%	5.4%	
	1	69	70	
	1.4%	93.2%	94.6%	
Age group (30-40 years)	6	2	8	0.001
	10.7%	3.6%	14.3%	
	1	47	48	
	1.8%	83.9%	85.7%	
BMI (<24.99 Kg/m2)	2	0	2	0.001
	2.0%	0.0%	2.0%	
	2	94	96	
	2.0%	95.9%	98.0%	
BMI (≥25.0 Kg/m2)	5	4	9	0.115
	15.6%	12.5%	28.1%	
	6	17	23	
	18.8%	53.1%	71.9%	

DISCUSSION

In recent times, there has been a growing focus on identifying pregnancy complications before they manifest symptoms. Endothelial dysfunction, often characterized by heightened levels of inflammatory markers, is more pronounced in women with preeclampsia compared to those with uncomplicated pregnancies. Among these markers, C-reactive protein (CRP) stands out as it is produced in response to stress, tissue damage, and various inflammatory markers.[11] In this study, we investigated the diagnostic accuracy of elevated C-reactive protein (CRP) levels in early pregnancy for predicting pre-eclampsia. A total of 130 patients participated, with a mean age of 28.16 ± 4.74 years and a mean body mass index (BMI) of 26.27 ± 5.05 kg/m^2. Comparing our findings with previous studies,

Aftab K *et al*.[12] reported a mean age of 29.69 ± 3.12 years in their study, with 113 (54.9%) of the patients having a BMI greater than 25 kg/m^2. Similarly, Babah OA *et al*.[13] found a mean age of 31.1 ± 4.51 years in their study, with preeclamptic subjects exhibiting a increased BMI (mean 30.04kg/m2 with standard deviation of 6.06 kg/m^2) in comparison to the women during pregnancy with normal blood pressure (28.08 kg/m^2 with standard deviation of 2.97 kg/m^2).

In this study, the sensitivity of CRP levels was found to be 81.8%, with a specificity of 97.5%. Comparatively, a recent study by Sharmin *et al*.[10] investigated the accuracy of CRP levels in predicting preeclampsia among pregnant females. They reported a sensitivity of 68.0% and specificity of 98.0% at a cut-off value of 5 mg/L for predicting the pre-eclampsia developments. Among the 150 patients screened for CRP levels, Sharmin *et al*. observed preeclampsia in 50 individuals (33.3%). Conversely, Gharib M *et al*[1] reported a sensitivity of 100% and specificity of 93.3% in their study. Furthermore, a systematic review conducted by Hamadeh R *et al*[14] indicated a consistent correlation in between the raised CRP concentrations and the onset of pre-eclampsia (PE) across 18 studies. This association was observed in individuals with a normal BMI (<25 kg/m2) in three studies and in overweight individuals in two studies. Additionally, the review also examined this association in individuals with a BMI ranging from 28 to 31 kg/m^2. Notably, three studies identified a threshold level of CRP above which a significant risk of developing PE should be considered.[14]

In comparison to our study, Kashanian M *et al*.[15] demonstrated that a serum hs-CRP level of 4 mg/L exhibited 78.1% sensitivity, 72.1% specificity, 25% PPV, 96.5% NPV, and 72.8% diagnostic accuracy. Additionally, hs-CRP levels surpassing 7 mg/L were identified among 26 (61.9%) of the patients of pre-eclampsia and 22 (6.25%) of the women with normal blood pressure during pregnancies, indicating a significant disparity (P = 0.001). However, divergent results have been reported in several other research studies regarding the relationship between CRP levels and preeclampsia.[16,17] Conversely, Sayyed AA *et al*[18] observed notably elevated concentrations of High-sensitivity C-reactive protein among patients with severe preeclampsia compared to those with mild preeclampsia, suggesting that HsCRP could serve as an indicator of preeclampsia severity.

A study conducted by Ismael HA *et al*[19] demonstrated significantly higher average serum levels of CRP in cases of severe preeclampsia (SPE) compared to non-severe preeclampsia (NSPE), indicating a substantial positive correlation between them. This suggests the involvement of inflammatory responses associated with both biomarkers in preeclampsia (PE), supporting their potential utility for assessing the severity of PE. However, our findings exhibited some disparities with certain other studies, possibly attributable to variations in factors such as sample size, selection criteria, timing of sample collection during pregnancy, and specific methodologies employed for CRP level detection. These methodological differences and variations in study design may contribute to the discrepant conclusions observed across studies investigating the relationship between CRP levels and preeclampsia. Given the potential implications for maternal, fetal, and neonatal health resulting from complications of PE, it is encouraged that the inclusion of CRP examination as a routine component of antenatal care. Nonetheless, we recommend conducting multicenter studies with larger study populations to enhance the accuracy of CRP in predicting the severity and onset of preeclampsia. Such endeavors would contribute to improving the management and outcomes of PE during pregnancy.

CONCLUSION

Based on the study conclusion, it is evident that elevated CRP levels during early pregnancy can serve as a significant marker for pre-eclampsia. Our analysis demonstrated a sensitivity of 81.8% and a specificity of 97.5% for elevated CRP levels in the prediction of pre-eclampsia. However, due to several limitations, these findings cannot be considered conclusive. It is recommended that healthcare providers consider incorporating CRP testing into their protocols for early pregnancy assessment, particularly for women at higher risk of developing pre-eclampsia. Additionally, further research is warranted to validate these findings across diverse populations and to explore the feasibility of implementing CRP screening on a broader scale within prenatal care settings. Such efforts may ultimately lead to improved early detection and management of pre-eclampsia, thereby reducing maternal and fetal morbidity and mortality associated with this condition.

LIMITATIONS

One limitation of our study was the relatively small sample size. Additionally, the association between elevated CRP levels in early pregnancy and the frequency of eclampsia was examined within a limited subset of women, potentially restricting the generalizability of our findings.

SUGGESTIONS / RECOMMENDATIONS

Additional research should be conducted to validate these findings across diverse populations and to evaluate the feasibility of implementing CRP screening on a broader scale in prenatal care.

CONFLICT OF INTEREST / DISCLOSURE

None.

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