ABSTRACT

Introduction: Preeclampsia is a hypertensive syndrome in pregnancy characterized by increased blood pressure, proteinuria, and complications such as liver dysfunction and visual impairment. This condition is associated with an inflammatory reaction and failure of trophoblast invasion of maternal arteries, which involves an increase in proinflammatory cytokines that indirectly induce CRP production. However, data showing the value of CRP levels as an indicator of the incidence of preeclampsia in Indonesia is minimal. This study aims to evaluate CRP levels as a predictor of preeclampsia.

Methods: This case-control study involved pregnant women with preeclampsia and normal pregnant women who went to the Obstetric Emergency Installation at Prof. Hospital. Dr. I.G.N.G Ngoerah Denpasar. All data were obtained from patient medical records and then analyzed using the SPSS v.22.

Results: This study involved 56 pregnant women consisting of 28 normotensive pregnant women (control) and 28 pregnant women with preeclampsia (cases) at Prof. Dr. I.G.N.G Ngoerah General Hospital Denpasar from January to December 2023. The median age was 27.5 years (control) and 26.0 years (cases), with an age range of 18–40 years. The median BMI WAS 21.65 kg/m² (controls) and 21.80 kg/m² (cases). Most patients in both groups were nulliparous (50.0%, controls; 42.9%, cases). Based on ROC analysis, the CRP cut-off value of 7.76 mg/dL has a sensitivity of 76.7%, specificity of 78.6%, and an area under the curve (AUC) of 0.737, where pregnant women with high CRP ($\geq$ 7.76 mg/dL) had a 12.048-fold higher risk (95%CI 3.496–41.515; p < 0.001) of experiencing preeclampsia compared to pregnant women with low CRP levels.

Conclusion: High serum CRP levels are a risk factor for preeclampsia. These findings indicate that measuring CRP levels can be a potential tool for identifying the risk of preeclampsia in the pregnant population.

Keywords: C-reactive protein (CRP), preeclampsia, risk factors.
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largest population in the world, still faces maternal health problems. Maternal Mortality Rate (MMR) indicates a country’s maternal health level. The maternal mortality rate in Indonesia is the third highest in Southeast Asia. Based on data from the Indonesian Demographic and Health Survey, MMR in Indonesia in 2012 was 359 per 100,000 live births. Hypertension in pregnancy is still one of the causes of maternal death in Indonesia. Some data from multicenter advanced health facilities shows that the incidence of hypertension in pregnancy reaches 17%. About 2% of them cause maternal death, and 12% of them cause perinatal death. Another study shows that the highest incidence of hypertension in pregnancy occurs in West Java Province, namely around 10.57% [6], [7].

Hypertension in pregnancy affects around 5%–10% of all pregnancies and is one of the leading causes of death and morbidity in pregnant women, especially preeclampsia. Preeclampsia is related to the failure of trophoblast invasion of the maternal spiral arteries, which causes an increase in uterine artery vascular resistance, thereby reducing uteroplacental blood flow [8]. Several studies report that there is a role of systemic inflammation in the development of preeclampsia, which involves proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). An increase in proinflammatory cytokines is also reported to stimulate the production of C-reactive protein (CRP), a protein produced during a systemic inflammatory reaction, a sensitive and objective marker for inflammation. C-reactive protein is produced by hepatocyte cells and increases at the start of infections, malignancies, and inflammation-related diseases [8]–[10]. As an inflammatory marker, C-reactive protein is produced by hepatocytes in response to systemic inflammatory reactions. Therefore, increased CRP levels may reflect the level of inflammation that occurs in preeclampsia [11]. Unfortunately, data showing the limit value of CRP levels as an indicator of the incidence of preeclampsia in Indonesia is still minimal.

This study aims to evaluate serum CRP levels as a reference value for preeclampsia predictors and determine the risk of preeclampsia due to high serum CRP levels.

2. METHODS

2.1. Study Design

This study was an analytical case-control study that compares CRP values in maternal blood serum. The case group was pregnancies with preeclampsia, and the controls were normal pregnancies. Then, the CRP values of the two groups were compared.

2.2. Population and Sample

The target population in this study was all pregnant women with or without preeclampsia in Bali Province. The population covered in this study were all pregnant women with or without preeclampsia who came to the Obstetrics Emergency Department at Prof. Hospital. Dr. I.G.N.G Ngoerah Denpasar from January 2023 to December 2023. The study sample was pregnant women with preeclampsia and normal pregnant women who went to the Obstetric Emergency Installation at Prof. Hospital. Dr. I.G.N.G Ngoerah Denpasar was selected by consecutive sampling from the accessible population after fulfilling the inclusion and exclusion criteria.

Inclusion criteria for the case group include 1) Pregnant women with gestational age above 28 weeks and have systolic blood pressure $\geq 140$ mmHg and diastolic $\geq 90$ mmHg, qualitative proteinuria $\geq +1$ or quantitative $\geq 0.3$ g/L in 24-hour urine; 2) Willing to participate in research voluntarily by signing a written informed consent. Inclusion criteria for the control group include 1) Pregnant women with gestational age above 28 weeks and have systolic blood pressure $< 140$ mmHg and diastolic $< 90$ mmHg, negative proteinuria. Meanwhile, the exclusion criteria were 1) Pregnant women with a history of hypertension before pregnancy or before 20 weeks gestation; 2) Pregnant women with a history of diabetes mellitus, cardiovascular disease, autoimmune disease, kidney disorders, uterine disorders, active smokers, and currently experiencing infections. The sample was selected sequentially (consecutive sampling) from pregnant women with preeclampsia and normal pregnant women who came to the Obstetric Emergency Installation at Prof. Hospital. Dr. I.G.N.G Ngoerah Denpasar from January 2023 to December 2023.

2.3. Variables and Data Collection

The independent variable in this study was CRP level, with the dependent variable being preeclampsia. Meanwhile, confounding variables include age, BMI, parity, and pregnancy with other diseases. CRP is defined as an acute-phase protein produced by the liver when the body is experiencing an inflammatory process. The CRP value is obtained using a 5-cc venous blood sample and will be checked using a reagent. According to ACOG, preeclampsia is a pregnancy disorder characterized by systolic blood pressure $\geq 140$ mmHg or diastolic $\geq 90$ mmHg on two examinations (minimum 4 hours apart) in pregnancies over 20 weeks in women who previously had normal blood pressure accompanied by proteinuria of 300 mg or more per 24-hour urine collection, a protein/creatinine ratio of 0.3 mg/dL, or a protein dipstick result of 2+. All data were obtained from patient medical records.

2.4. Data Analysis

Data was analyzed using the SPSS for Windows version 22.0 program on the test variables. The cut-off value for CRP levels was determined using the receiver operating characteristic (ROC) curve. The cut-off value for CRP levels is determined based on the H-score cut-off point on the ROC with the best area above the curve (AUC), sensitivity and specificity levels. Based on this cut-off value, CRP levels will be grouped into high CRP levels and low CRP levels. Bivariate analysis between categorical sample characteristics and the incidence of preeclampsia was carried out using the Chi-Square or Fisher’s exact test. In contrast, bivariate analysis between numerical sample characteristics and the incidence of preeclampsia was carried out using the T-test (if normally distributed) or the Mann-Whitney test. U (if it is not normally distributed).
In accordance with the journal’s guidelines, we will provide our data for independent analysis by a selected editorial team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

3. Results

3.1. Baseline Characteristics

This study involved 56 pregnant women consisting of 28 normotensive pregnant women (control) and 28 pregnant women with preeclampsia (cases) at Prof. Dr. I.G.N.G. Ngoerah General Hospital Denpasar from January to December 2023. The characteristics of research subjects assessed in this study include age, BMI, and parity, which are risk factors for preeclampsia in pregnant women. Based on the normality test carried out using the Kolmogorov-Smirnov test, these three characteristics are generally not distributed (p < 0.05); thus, the distribution of these characteristic data is displayed in the form of median and minimum (min) and maximum (max) values (Table 1).

The median age of the case group was 27.5 years with an age range of 18–40 years, while the median age of the control group was 26.0 years with an age range of 18–40 years. The median BMI both the case and control groups, showed similar results, namely 21.65 kg/m² and 21.80 kg/m², respectively. Most of the patients in the group of pregnant women with preeclampsia were nulliparous (50.0%). Furthermore, in the preeclampsia group, 7 patients were primiparous (23.3%), and 8 were multiparous with a parity of 2 to 3 (26.7%). Similar to the group of pregnant women with preeclampsia, the majority of patients in the normotensive group were also nulliparous (42.9%). As many as 32.1% of patients in the group of pregnant women without preeclampsia were primiparas, and another 25.0% of patients were multiparas. Thus, based on the results of the Mann-Whitney U test, it can be concluded that there are no differences in characteristics (age, BMI, and parity) between pregnant women with preeclampsia and pregnant women without preeclampsia (p > 0.05).

3.2. High Serum CRP Levels as a Risk Factor for Preeclampsia

CRP levels are also displayed in the form of median values and min-max values because CRP level values were also found to be not normally distributed based on the Kolmogorov-Smirnov test (p < 0.05). It was found that the group of pregnant women with preeclampsia had a significantly higher median CRP level compared to normotensive pregnant women (30.30 mg/dL vs. 4.06 mg/dL; p = 0.002). Therefore, we can conclude that CRP levels are significantly related to the incidence of preeclampsia (Table II).

In this study, we analyzed CRP value data using the ROC curve to obtain the CRP cut-off value with the best sensitivity and specificity used to predict the incidence of preeclampsia (as shown in Fig. 1). The results of the ROC curve analysis of the CRP value show that a CRP value of 7.76 mg/dL is the best cut-off value with a sensitivity of 76.7%, specificity of 78.6%, and an area under the curve (AUC) of 0.737 (95% CI 0.60–0.87; p = 0.002) (Fig. 1). CRP values were grouped based on predetermined cut-off values into high CRP levels (≥7.76 mg/dL) and low CRP levels (<7.76 mg/dL). Table III shows that high CRP levels were more frequently found in pregnant women with preeclampsia (23 pregnant women) compared to the group of normotensive pregnant women (6 pregnant women). Based on the Chi-square test, it was found that high CRP levels (≥7.76 mg/dL) in pregnant women were a significant risk factor for preeclampsia, where high CRP levels increased the risk of preeclampsia in pregnant women up to 12 times higher (OR 12.048; 95% CI 3.496–41.515; p < 0.001).

4. Discussion

Preeclampsia is a disorder in pregnancy that is associated with new-onset hypertension that occurs at a gestational age above 20 weeks. Until now, the exact pathogenesis of preeclampsia is still unknown and is thought to be multifactorial. Various studies have examined risk factors for preeclampsia, where maternal age, parity, body mass index, previous history of hypertension, and maternal comorbidities are among the risk factors found to be strongly associated with the incidence of preeclampsia [12], [13].

The results of this study prove that there is a significant relationship between serum CRP levels and the incidence of preeclampsia, where the median CRP level in pregnant women with preeclampsia is significantly higher compared to normotensive pregnant women (30.30 mg/dL vs. 4.06 mg/dL; p = 0.002). Savadi et al. also showed that there was a significant difference in CRP levels between pregnant women with preeclampsia and healthy normotensive pregnant women, where higher CRP levels were found in pregnant women with preeclampsia (7.54 ± 2.44 mg/dL vs. 5.8 ± 3.0 mg/dL, p < 0.001). Additionally, Savadi et al. also found a moderate positive correlation between CRP levels and systolic (r = 0.523) and diastolic (r = 0.528, p < 0.001) blood pressure in the group of pregnant women with preeclampsia so it can be concluded that CRP can also be used as a predictor of severity [14]. This is also proven by the study of Sayyed et al. (2020) involving 50 pregnant women with preeclampsia and 50 healthy
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TABLE II: CRP Values Difference between Cases and Control Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preeclampsia (n = 28)</th>
<th>Normotensive (n = 28)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/dL)</td>
<td>30.30 (1.00–172.30)</td>
<td>4.06 (1.00–87.30)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Fig. 1. Receiver operating curve (ROC) curve of CRP values.

TABLE III: CRP Levels as a Risk Factor for Preeclampsia in Pregnant Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preeclampsia (n = 28)</th>
<th>Normotensive (n = 28)</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP value (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (≥ 7.76)</td>
<td>21</td>
<td>76.6</td>
<td>6</td>
<td>21.4</td>
<td>12.05</td>
</tr>
<tr>
<td>Low (&lt;7.6)</td>
<td>7</td>
<td>23.4</td>
<td>22</td>
<td>78.6</td>
<td></td>
</tr>
</tbody>
</table>

Note: *Significant in p < 0.05.

normotensive pregnant women. Sayyed et al. proved that significantly higher CRP levels were found in the group of pregnant women with preeclampsia compared to healthy normotensive pregnant women (3.09 ± 1.77 mg/dL vs. 1.47 ± 0.59 mg/dL, p < 0.001). The study of Sayyed et al. even found a strong and significant correlation between systolic (r = 0.67) and diastolic (r = 0.71, p < 0.001) blood pressure and CRP levels [15]. The study of Perveen et al. also showed a significant difference in serum CRP levels between pregnant women with preeclampsia and healthy pregnant women with higher serum CRP levels in pregnant women with preeclampsia (5.30 ± 2.75 vs. 3.13 ± 1.28, p < 0.001) [11]. The study of Meena et al. also found that CRP levels were significantly higher in pregnant women with preeclampsia, especially in more severe preeclampsia (2.68 ± 0.9 mg/dL in normotensive pregnant women, 13.22 ± 0.88 mg/dL in pregnant women with mild preeclampsia, and 17.58 ± 0.9 mg/dL in pregnant women with severe preeclampsia (p < 0.0001) [16].

The half-life of CRP is around 19 hours and CRP is metabolized relatively quickly so that CRP levels will also decrease when preeclampsia has resolved [17], [18]. The study of Sayyed et al. also showed a correlation between higher serum CRP levels and the severity of preeclampsia, where CRP levels were found to be 1.47 ± 0.59 mg/L in normotensive pregnant women, 2.89 ± 1.12 mg/L in pregnant women with mild preeclampsia and 4.3 ± 0.58 mg/l in severe preeclampsia (p < 0.001). Based on this, there are suggestions regarding using serum CRP levels to predict preeclampsia. However, until now, there is still debate regarding the optimal cut-off value for serum CRP levels as a predictor of preeclampsia in pregnant women. Based on the results of the ROC curve from the CRP value in this study, the optimal cut-off value for CRP was 7.76 mg/dL, with a sensitivity of 76.7% and a specificity of 78.6%. By using this cut-off value, it was found that high CRP levels (≥ 7.76 mg/dL) increased the risk of preeclampsia in pregnant women up to 12 times.
higher (OR 12.048; 95%CI 3.496–41.515; p < 0.001). Similar to the results of this study, the study of Gencheva et al. also found that higher hs-CRP levels increased the risk of preeclampsia by up to 3.3 times (OR 3.31; CI95% 1.32–8.29) but this study used the optimal cut-off value of serum CRP levels for predicting preeclampsia which is different, namely 5,446 ng/ml or the equivalent of 0.5446 mg/dL. The cut-off value has a sensitivity level productivity of 72% and specificity of 56% (AUC 0.548; p = 0.445) [19]. Another study by Jannesari et al. obtained the optimal cut-off value for high-sensitivity C-Reactive Protein (hs-CRP) of 5.24 ng/mL with a sensitivity level of 62.7% and specificity of 54%. Still, this study did not carry out the bivariate analysis. It only showed significant differences in serum CRP levels with higher serum CRP levels found in women with preeclampsia [20]. The study of Gharib et al. also showed that higher serum HsCRP levels were significantly associated with the incidence of preeclampsia (p < 0.001). Still, that study used different hs-CRP cut-off values. The study of Gharib et al. used a cut-off serum hs-CRP level of 15.5 mg/dL with a sensitivity of 93.9% and a specificity of 73.3% [21]. Although using different cut-offs, all these studies show that hs-CRP predicts preeclampsia with quite good sensitivity and specificity values. The hs-CRP cut-off value obtained varies between studies because this value is obtained through ROC curve analysis, so there are differences in population and measuring instruments between studies, producing different cut-off values [22], [23]. Therefore, large-scale, multicenter research involving different races and ethnicities is needed to determine a universal and standardized cut-off value for serum CRP levels as a predictor of preeclampsia.

This study has several advantages. First, all factors that can influence CRP levels, such as a history of hypertension before pregnancy, the presence of comorbid heart disease, diabetes mellitus, kidney disorders, and other infectious diseases, have been controlled through the research design so that bias in measuring CRP levels can be minimized in this study. In addition, sample selection was carried out well so that there were no differences in baseline characteristics (age, BMI, and parity) between pregnant women with preeclampsia and normotensive pregnant women so that the influence of maternal age, parity, and obesity on the incidence of preeclampsia and CRP levels in this study can be removed. However, this study had a small sample size and was only conducted in one center, so the results may not apply to pregnant women of different races and ethnicities. In addition, the weakness of the case-control study design in this study is its retrospective nature, which may cause recall bias during the data collection process.

5. Conclusion

Based on the results obtained in this study, we can conclude that high serum CRP levels are a risk factor for preeclampsia, with a CRP value of 7.76 mg/dL. However, interpretation of CRP levels must be done carefully due to several conditions that can also cause an increase in CRP levels in pregnant women, including comorbid diabetes mellitus, heart disease, kidney disease, and other infectious diseases. Furthermore, future research is needed with a prospective, large-scale, multicenter design to obtain a standardized cut-off value for serum CRP levels and the optimal timing for checking serum CRP levels as a predictor of preeclampsia in pregnant women.

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Author Contributions

Conception of the study: AANJK, IMD, ESW. Methodology and investigation: ESW, IGBAM. Dataset preparations (software) and variables revision: AANJK, IMD, ESW, IGBAM. Data collection and interpretation individually by each center (resources): AANJK, IMD, IGBAM. Data validation and curation: AANJK, IMD, ESW, IGBAM. Formal statistical analysis: AANJK, ESW, IGBAM. Writing-original draft: AANJK, IMD, ESW, IGBAM. Writing-review and editing: all authors. Supervision: AANJK. Project administration: all authors. Final approval of manuscript: all authors. Guarantor: AANJK.

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Ethics Approval

This study has obtained Ethical Eligibility from the Research Ethics Commission of the Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G. Ngoerah General Hospital Denpasar, dated January 18, 2023, Number 39/UN14.2.2.VII.14/LT/2023 and obtained a Research Permit from the Education and Research Section of Prof. Dr. I.G.N.G. Ngoerah General Hospital Denpasar dated April 26, 2023, Number DP.03/D.XVII.2.2.2/18606/2023.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

References

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