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Original Research Article

Platelet to Lymphocyte Ratio as a New Inflammation Marker for the Preterm PROM

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Abstract

Premature rupture of membranes (PROM), also known as "pre-labour rupture of membranes," occurs when the gestational membranes burst after 37 weeks but before labor really starts. This study showed that PLR could be a new inflammatory marker for diagnosing preterm PROM. The study place was the Department of Obstetrics and Gynaecology, Sir Salimullah Medical College (SSMC) & Mitford Hospital (MH), Dhaka, Bangladesh, from May 2019 to October 2019. It was a case-control study. All mothers were selected by purposive sampling who were PPROM as cases. Age-matched non-PPROM pregnant women at term were also enrolled as control. Afterward, they were scrutinized according to eligibility criteria, and 200 mothers were enrolled. Among them, 100 were cases, and the other 100 were in control. A pre-tested, observation-based, peer-reviewed data collection sheet was prepared before the study. Data regarding clinical, biochemical, and surgical profiles were recorded. Data were compiled, edited, and analyzed. The P-value was determined by the chi-square test (categorical variables) and the student's t-test (continuous variables). The p-value was significant at <0.05. The mean age of 100 patients from the case was 24.39±2.81 (age range: 18-36) years, and that of the control, like 100 normal pregnant women, was 24.31±2.34 (age range: 19-35). (P=0.49). The mean parity of case and control were 2.1±0.9 (range: 0- 5) and 1.98±0.2 (range: 0-3). The mean gravida of case and control were (3.1±1.2 vs. 3.4±1.4).The platelet count was found significantly higher in PROM or cases (241.6±58.7 vs 201.7±65.9 $x1000/mm^3$, p <0.001). PLR was higher (125.8±67.1 vs 105.2±48.6) in cases (P<0.001). So, *there is a good opportunity to utilize PLR as an* inflammatory marker to predict preterm *PROM. PLR* is used in many acute or chronic inflammatory conditions. Its use to predict preterm PROM is a new concept. For that reason, this study is rational and time demanding.

Keywords: Platelet, Lymphocyte, PROM, Preterm, Inflammatory, Biomarker.

INTRODUCTION

Preterm PROM (PPROM) is the natal used to describe membrane rupture that occurs before 37 weeks of gestation. The bulk of neonatal morbidity and mortality is attributed to prematurity. Preterm (PROM) deliveries are more challenging to handle. Membrane rupture that occurs prior to labor is distinguished by its short latency, increased risk of intrauterine infection, and increased likelihood of umbilical cord compression. Chorioamnionitis and placental abruption are more likely to occur in women with preterm PROM [1].

Platelets are small anucleated cell which are cytoplasmatic fragments of bone marrow megakaryocytes, with a diameter of 3-5μm and a volume of 4.5–11 Femto liter (Fl). A single megakaryocyte can give rise to 1500–2000 of them to the bloodstream, where they circulate for 7–10 days [2]. Platelets are dynamic blood particles whose primary function, along with the coagulation factors, is hemostasis, or the prevention of bleeding. Platelets interact with each other, as well as with leukocytes and endothelial cells, searching the vascular bed for sites of injury. There, they become activated and when stimulated, platelets undergo a shape change and their surface area increases. Platelets play a crucial role in the initial stages of clot formation by sticking to damaged blood vessels and contributing their membrane phospholipids for the activation of coagulation factors [3]. In addition to their important role

in hemostasis and thrombosis, accumulating evidence demonstrates that platelets contribute to the inflammatory process, microbial host defense, wound healing, angiogenesis, and remodeling [4]. Platelet indices, such as mean platelet volume (MPV) and platelet distribution width (PDW), platelet large cell ratio (PLCR) are a group of derived platelet parameters obtained as a part of the automatic complete blood count.

Emerging evidence suggests that platelet indices may have diagnostic and prognostic value in certain diseases [5]. Platelets indices have been recently used in the prediction, diagnosis, and prognosis of many diseases being reported as clinically useful biomarkers; important indications are preterm PROM and preeclampsia [6]. Thrombocytopenia is attributed to two main causes. Failure of platelet production and early excessive platelet consumption [6].

Platelets and lymphocytes share regulatory mechanisms in the pathophysiology of thrombosis, inflammation, immunity, and atherosclerosis. The effect of platelets on lymphocyte function may be via direct contact or by soluble mediators [7]. Platelets enhance adhesion and cell migration of lymphocytes, and affect other functional aspects of lymphocytes in a complex manner [8].

In chronic inflammatory processes, megakaryocytic series proliferate increasingly and lymphocyte counts tend to decrease due to severe apoptosis. As a consequence, markers obtained from total blood counts such as the platelet- to-lymphocyte ratio (PLR) can be affected in severe chronic inflammatory diseases [9].

PLR is an effective and simple marker. It has been proposed as a predictive and prognostic parameter for many kinds of diseases such as cardiovascular diseases and malignancies [10]. Also, it has been shown to be related with gestational diabetes mellitus, acute appendicitis, preeclampsia, recurrent pregnancy loss, and preterm labour in pregnant women [11]. There are scanty data about the relation between PLR and presence of preterm PROM in the literature. The main aim of this study is to relate platelet to lymphocyte ratio as a marker for preterm PROM.

MATERIALS & METHODS

Women with preterm PROM who attended the Department of Obstetrics and Gynecology at Sir Salimullah Medical College & Mitford Hospital in Dhaka, Bangladesh, from May 2019 to October 2019 were the subjects of this study.

The sample size for this case-control research is established using the following formula.

$n = (Z_\alpha + Z_\beta)^2 \times (\sigma_1^2 + \sigma_2^2) / (\mu_1 - \mu_2)^2$

All values were from[12]

n = desired sample size

μ_1 = mean of control group = 106.9

μ_2 = mean of PRETERM PROM group =126.3

σ_1 = SD of control group = 49.4

σ_2 = SD of PRETERM PROM group =68.9

Z_α = Z- Value at a definite level of significance, e.g., 3.90 at 0.01% level of significance

$Z\beta$ = Z-value at a definite power, e.g., 2.33 at 99% power (when $\beta = 0.01$)

Putting the values therefore we get,

$n = (3.90 + 2.33)2 \times (49.42 + 68.92) / (106.9 - 126.3)2$

$=39.9424 \times (2440.36+4747.21)/376.36$

$= 762.80$

$= 762$

But, due to time constraints, 200 cases were enrolled in the study (100 in case and 100 in control).

Sampling Methods

In order to assess PLR as an inflammatory marker to identify preterm PROM, the method of choice for selecting the sample from the women visiting the Gynecology & Obstetrics department of SSMC&MH during the earlier mentioned study period was purposeful sampling.

Preterm PROM patients (cases), age-matched term non-PROM pregnant women (control), and mothers who agreed to participate in the study were the inclusion criteria.

Exclusion criteria were multiple gestations, hematologic disorders, malignancies, hepatic disease, history of autoimmune disease, any inflammatory disease of pregnancy such as gestational diabetes mellitus and preeclampsia, any acute or chronic infectious or inflammatory diseases, pregnancies with fetal chromosomal anomalies, intrauterine growth restriction, fetal infection, and women who will undergo any invasive procedures such as amniocentesis.

Study Procedure

One hundred pregnant women with preterm PROM and 100 age-matched pregnant women at term were enrolled by purposive sampling in this prospective case-control research. A pre-structured sheet for gathering data was created. A thorough history and physical examination, including per speculum examination, was performed to examine cases and maintain control carefully. Preterm PROM patients and term pregnant controls were the same people. Data regarding socio-demographic, obstetrics, and hematological profile was recorded. Age, gestational week, gravida, parity, delivery mode, birth weight, APGAR score, neonatal intensive care unit (NICU) admission rate, presence of neonatal sepsis, and development of respiratory distress syndrome (RDS) was recorded. In addition, the results of a complete series of routine laboratory investigations, including complete blood cell counts, were recorded. Complete blood counts

were analyzed using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland INC, Mervue, Galway, Ireland). The platelet- to-lymphocyte ratio (PLR) was calculated by dividing the platelet count by the lymphocyte count. Randomization and blinding methods were not applicable. The equipment used in the study were clinical records, observation, investigation reports, and questionnaires. We collected data by interviewing through preformed structured questionnaires.

Main Outcome Variables

Table 1: Distribution of the variables

Independent variables		
Socio-demographic profile	***Obstetric profile***	***Hematological profile***
Age	Parity	Platelet count
Income status	Duration of amenorrhea	Lymphocyte count
Area of Residence	Gravida	PLR
Dependent variables		
Platelet to lymphocyte ratio as a marker of preterm PROM		
Confounding variable (NA) Selection bias may be act as a confounding factor.		

Procedures of Data Analysis and Interpretation

After being collected, all data were reviewed and modified. Then, using a Windows 7 spreadsheet, we created charts. All continuous variables' frequency distributions and normal distributions were then computed. Cross- tabulation was then created. Version 23 of SPSS was used. P values<0.5 were considered significant.

Ethical Implication

Children, young people, and seriously ill convicts were all excluded from the study. The sample unit was informed of the process and told that it would not affect their ability to get therapy if they chose not to participate in the study. They have the option to leave the study at any time if they so choose throughout it. The patient's signed informed permission was obtained. Additionally, the concerned department where the study was conducted has given its written consent.

RESULTS

A case-control study was conducted with a total of 200 enrolled patients. Among them, 100 were cases with preterm PROM & 100 were controlled and were term pregnancies without complications.

Table 2: Demographic variables representation (N=200)

Variables	**Case (n=100)**	**Control (n=100)**	**P-value**
Age (in years) (Mean ± SD)	24.392.81	24.31±2.34	0.49^{NS}
Range (in years)	18 – 36	19 – 35	
Parity	2.1±0.9	1.98±0.2	0.35^{NS}
Range	0 – 5	0 – 3	
Area of residence	(n, %)	(n, %)	
Urban	22 (%)	14 (%)	-
Rural	78 (%)	86 (%)	
P-value was calculated by student's t test (continuous variables) and chi square test (categorical variable), NS: Not significant, P-value was significant at <0.05			

Table 2 shows that in terms of the mean age and parity case and control match with each other and p-value is not significant.

Obstetric Profile (N=200)

Table 3: Obstetric profile of the respondents (N=200)

Obstetric profile	**Case (n=100)**	**Control (n=100)**	**P-value**
Gravida (n)	3.1±1.2	3.4±1.4	**0.53^{NS}**
Para (n)	2±1.3	1.9±1.4	**0.16^{NS}**
Gestational age (week)	33.6±2.5	37.3±0.29	**0.86^{NS}**
P-value was calculated by student's t test, NS: Not significant, P-value was significant at <0.05			

Table-3 shows that there was no statistically significant difference between case and control regarding mean gravida (3.1±1.2 vs 3.4±1.4), mean para (2±1.3 vs 1.9±1.4) and mean gestational age (33.6±2.5 vs 34.7±1.2) (P=>0.05).

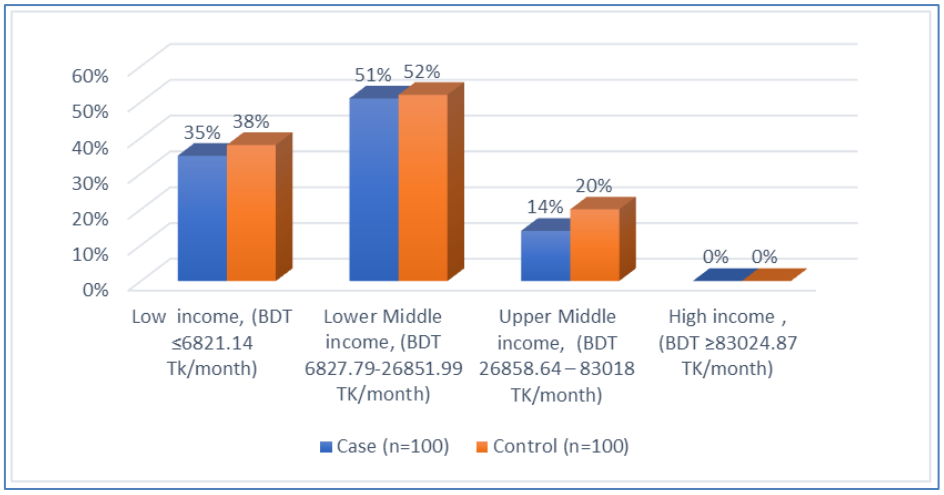

Figure 1: Distribution of the study subjects by socioeconomic status according to World Bank Data Team (N=200)

(Figure 1) shows that 51%, 35% and 14% in cases and 52%, 38% and 20% in control come from lower middle income, low income and upper middle income group respectively.

Hematological Profile (N=200)

Table 4: Hematological profile of the respondents (N=200)

Hematological profile	Case (n=100)	Control (n=100)	P-value
WBC Count (/mm^3)	9.1(6.31 – 10.7)	8.8 (6.1 – 9.9)	**0.85^{NS}**
Lymphocyte count (/mm^3)	1896.7±651.8	2144.7±673.2	**0.5^{NS}**
Platelet count (×1000/mm^3	241.6±58.7	201.7±65.9	**<0.001^{S}**
PLR	125.8±67.1	105.2±48.6	**<0.001^{S}**
P-value was calculated by student's t test, S: Significant, NS: Not significant, P-value <0.05 was significant			

Table-4 shows that the platelet count was found to be significantly higher in PROM or cases than in the control (241.6±58.7 vs 201.7±65.9×1000/mm^3, p <0.001). PLR is also higher in cases (P=<0.001).

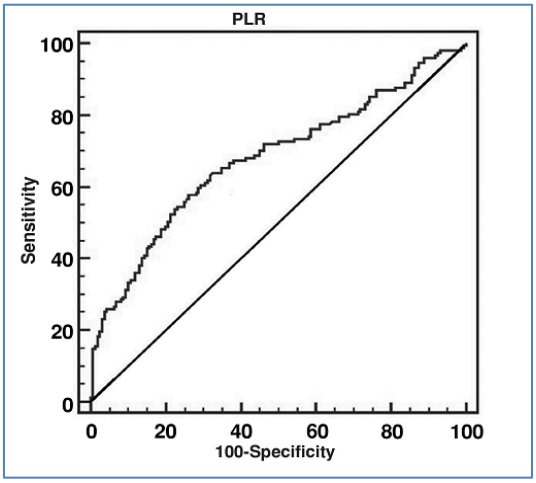

Figure 2: Receiver operating curve for PLR for the diagnosis of preterm PROM

Figure-2 shows that the ability of the PLR to diagnose preterm PROM according to ROC curve analysis is like following. The AUC for PLR was 0.6 (P=<0.001). The sensitivity and specificity of the PLR was 57% and 74.5% respectively, at a threshold >117.14. PLR values >117.14 were significantly related with increased risk of preterm PROM.

DISCUSSION

In this study, the cases and controls were matched. None of the sociodemographic variables between case and control showed statistically significant difference (P=>0.05). The mean age of cases was 24.39±2.81 years and that of the controls were 24.31±2.34 years (table 2). These findings were similar to the findings found in the study done by Endale *et al.*,

[13]. Mean parity of case and control were 2.1±0.9 (range:0-5) and 1.98±0.2 (range: 0-3) respectively. There was no statistically significant difference (P=>0.05) in mean of gravida, para and gestational age between cases and controls. These findings were consistent with the Turkish study done by Jaffar DW *et al.,* [14]. Socio-economic status of cases and controls were matched each other (figure 1). Most of the patients were in the lower middle-income group. Endale *et al.,* [13], found the same findings in their study.

In this study Platelet count was found to be significantly higher in preterm PROM group (case) than control (241.6±58.7×1000/mm³ vs 201.7±65.9 ×1000/mm³). P value is <0.001 which is statistically significant. This is supported by the studies done by Satar *et al.,* [15], and Flídrová and Krejsek [16]. Satar *et al.,* [15], reported that interleukin (IL)-8 levels were increased in preterm PROM in maternal serum and in the umbilical cord blood. Similarly, IL-6 was found elevated only in the umbilical cord blood, especially in preterm PROM with microbial invasion and histologic chorioamnionitis. In the study of Flídrová and Krejsek [16], cytokines such as tumor necrosis factor (TNF)-α, IL-8, IL-6, and IL-1, were reported to be increased in preterm birth and preterm labour.

Lymphocyte count in case and control group was 1896.7±651.8/mm³ and 2144±673.2/mm³ respectively. P value is 0.5 which is not statistically significant. This finding is similar with the study done by Toprak E *et al.,* [17], and Klement AH *et al.,* [18].

PLR (platelet to lymphocyte ratio) is a widely-used inflammatory marker. PLR has been recognized as one of the strong predictor of systemic inflammation, particularly in chronic inflammatory diseases. It is a good indicator of platelet activation, lymphocyte function and immune response. In chronic inflammatory process, platelet count proliferates increasingly and lymphocyte counts tend to decrease due to apoptosis. As a result, PLR value is affected in inflammatory process. It has been demonstrated that PLR predicts thrombotic events, inflammatory diseases, and malignancies and preterm PROM. In pregnant women, PLR was investigated in gestational diabetes, acute pancreatitis, preeclampsia, and preterm PROM (Ekin A *et al.,* [19], YucelB *et al.,* [20], Dadhich S *et al.,* [21].

In this study, PLR was significantly higher in preterm PROM group (cases) in comparison to controls, irrespective of the latency period and amniotic fluid index. P value is <0.001 which is statistically significant. These findings were strongly supported by the study done by Toprah *et al.,* [17], and Ekin A *et al.,* [22].

Toprah *et al.,* [17], found PLR was significantly higher in patient with preterm PROM than the control group who were patient with preterm labour. In preterm PROM, Ekin *et al.,* [19], found that the PLR showed no significant alteration between oligohydramnios and normal amniotic fluid index groups. Another study done by Ekin A *et al.,* [22], which investigated the relationship between PLR (platelet to lymphocyte ratio) and preterm PROM. It was designed regarding the latency period. PLR was not found to be significantly different between latency periods of <72 hours and >72 hours in preterm PROM and chorioamnionitis.

The ability of PLR to predict preterm PROM was evaluated using receiver operating curve (ROC) analysis. The AUC for PLR was 0.6 (P <0.001). The sensitivity and specificity of the PLR was 57% and 74.5% respectively, at a threshold >117.14. Platelet to lymphocyte ratio (PLR) values >117.14 were significantly related with increased risk of preterm PROM in the absence of clinically evident sepsis. These findings were strongly supported by the study done by Toprak E *et al.,* [17]. In this study ROC curve analysis showed that AUC for PLR was significant (P<0.001). It showed an important correlation between PLR and the occurrence of preterm PROM.

CONCLUSION

According to this study, the PLR (platelet to lymphocyte ratio) greatly influences preterm premature membrane rupture. It can aid in identifying those who are susceptible to early preterm PROM. PLR has been shown to predict preterm PROM, inflammatory illnesses, cancers, and thrombotic events. So, PLR can make it possible to manage preterm labor appropriately and prevent the adverse effects of preterm PROM on the fetus and the mother.

Limitations of the Study

The study period had a brief duration. If the study period had been longer, it would have been great if the study could have been discovered. Besides, it was a single-centered study with a modest sample size.

RECOMMENDATIONS

A multi-centered study may be carried out for different divisional/tertiary hospitals in Bangladesh. Prolonged research is advised. The most accurate marker for preterm PROM will be made clear by comparison research incorporating the many inflammatory biomarkers such as NLR (neutrophil to lymphocyte ratio), PLR (platelet to lymphocyte ratio), and CRP (C Reactive Protein).

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