

C-Reactive Protein as a Predictor of Chorioamnionitis

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Context: Chorioamnionitis (CAM) affects many pregnancies complicated by preterm premature rupture of membranes (PPROM). Finding a serum factor that could accurately predict the presence of CAM could potentially lead to more efficient management of PPRM and improved neonatal outcomes.

Objective: To determine if C-reactive protein (CRP) is an effective early marker of CAM in patients with PPRM.

Methods: A retrospective evaluation of pregnant women with PPRM at Geisinger Medical Center in Danville, Pennsylvania, between January 2005 and January 2009. Nonparametric statistical tests (ie, Wilcoxon rank sum and Spearman rank correlation) were used to compare distributions that were skewed. Characteristics of the study population were compared using 2-sample *t* tests for continuous variables and Fisher exact tests for discrete variables. Logistic regression analysis was used to generate receiver operating characteristic curves and obtain area under the curve estimates in stepwise fashion for predicting histologic CAM. A secondary analysis compared the characteristics among patients with clinical CAM, histologic CAM, or non-CAM.

Results: The total population of 73 women was subdivided into patients with histologic CAM (n=26) and patients without histologic CAM (ie, no evidence of CAM on placental pathology; n=47). There was no difference between groups in CRP levels, days of pregnancy latency, white blood cell count, smoking status, antibiotic administration, or steroid benefit. The group with histologic CAM delivered at earlier gestational ages: mean (standard deviation) age was 29.5 (4.4) weeks vs 31.9 (3.5) weeks ($P=.02$). For our primary analysis, we found no difference in CRP levels ($P=.32$). Receiver operating characteristic curve plots of CRP levels, temperature at delivery, and white blood cell count resulted in an area under the curve estimate of 0.696, which was 70% predictive of histologic CAM. In the secondary analysis, after adjusting for gestational age, the estimated hazard ratio for CRP change was 1.05 (95% confidence interval, 1.02-1.08; $P=.001$). Therefore, increasing CRP levels from PPRM was statistically significant in predicting clinical CAM development over time.

Conclusion: C-reactive protein levels were not effective independent predictors of clinical or histologic CAM, nor was sequential CRP testing statistically significant for the identification of clinical or histologic CAM in patients with PPRM.

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Clinical chorioamnionitis (CAM), which is diagnosed before delivery using only clinical findings, complicates 0.5% to 10% of pregnancies¹ and is considered a risk factor for increasing rates of perinatal death, neonatal respiratory distress syndrome, and neonatal infection.² Histologic CAM refers to CAM that is confirmed after delivery by means of histologic evaluation, which detects pathogens in usually sterile tissues. Studies^{3,4} of long-term outcomes in neonates born with an intra-amniotic infection such as CAM have shown an increased relative risk of cerebral palsy and cystic periventricular leukomalacia. Traditionally, clinical CAM diagnosis is dependent on findings such as leukocytosis (white blood cell [WBC] count, $>15,000/\mu\text{L}$), fetal tachycardia, maternal fever (temperature, $>100.4^\circ\text{F}$), fundal or uterine tenderness, or foul-smelling amniotic fluid.⁵ Amniocentesis may be used to detect subclinical

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infections in patients. In addition to culturing the amniotic fluid to identify microbial colonization, the fluid can also be evaluated by Gram stain to measure WBC counts and glucose levels. Other laboratory values may act as markers of intrauterine infection before clinical symptoms emerge. These markers would help to stem systematic, unidentified infection in preterm neonates and allow for prompt identification of early or subclinical intrauterine infection leading to more timely delivery. Patients with preterm premature rupture of membrane (PPROM) would then be treated with antibiotic and steroid administration.

We hypothesized that C-reactive protein (CRP) levels may be a marker of CAM prior to its clinical expression. C-reactive protein is an acute-phase protein that tends to be elevated in patients with systemic cases of inflammation. It is produced by the liver and binds to phosphocholine on microbes to assist in complement binding to damaged or foreign cells, serving as an early defense against infection. This process in turn promotes enhancement of phagocytosis of macrophages. Previous studies⁶⁻⁸ have associated elevated CRP levels with preterm parturition. Nevertheless, a subsequent systematic review⁹ of 5 studies challenged the use of CRP levels as a marker associated with clinical CAM in patients with PPRM, concluding that CRP level was an insubstantial marker associated with clinical CAM.

Because some studies⁶⁻⁸ in the obstetrical literature associated preterm delivery with elevated CRP levels, our institutional protocol encouraged regular testing of CRP at hospital admission for patients with PPRM. It mandated obtaining WBC count and CRP level on a daily basis for the first 3 days after admission, followed by WBC count and CRP level assessment twice weekly until delivery. Therefore, our main objective was to determine whether measuring individual or sequential CRP levels was useful for diagnosing CAM before onset of traditional clinical symptoms. The current study is a retrospective analysis of 4 years of data involving patients with PPRM.

Methods

Study Population

Pregnant women with a diagnosis of clinical CAM, histologic CAM, or both and PPRM as identified in *International Classification of Diseases, Ninth Revision*, were included in this retrospective study of medical records at Geisinger Medical Center (GMC) in Danville, Pennsylvania, between January 1, 2005, and December 31, 2008. The GMC Institutional Review Board approved the project protocol.

Patients from 20 to 37 weeks of gestation were included in the analysis if they had prenatal care at GMC or delivered at a GMC facility within the study period. Patients were excluded if their electronic medical records lacked CRP data or if their medical records, on subsequent review,

contained data that overturned the diagnosis of PPRM. We reviewed each medical record for the following variables: maternal age, race, gestational age, maternal smoking status, Gram stain and culture results, steroid administration, administration of antibiotics for latency, WBC count during pregnancy closest to the delivery date, CRP levels before delivery, temperature at onset of labor, and days of latency from time of PPRM to delivery.

A secondary analysis was performed to determine if there were any substantial differences in patients whose CAM was diagnosed in the antepartum period based on clinical factors alone (ie, from medical record review) and not proven after birth by histologic findings of CAM (ie, from placental evaluation). The control group comprised patients with neither clinical nor histologic CAM.

Statistical Analysis

For our primary analysis, all variables of the patients with PPRM were compared by means of histologic CAM status. Nonparametric statistical tests (Wilcoxon rank sum and Spearman rank correlation) were used to compare distributions that were skewed; these variables were then summarized using median (interquartile range [IQR]). Otherwise, characteristics of the study population were compared using 2-sample *t* tests for continuous variables, summarized using mean (standard deviation [SD]), and analyzed using Fisher exact tests for discrete variables. Logistic regression analysis was used to generate receiver operating characteristic (ROC) curves and to obtain area under the curve (AUC) estimates in stepwise fashion for predicting CAM status. The ROC curves are shown in the *Figure* and plott CRP level only (line A), CRP level plus maternal temperature at delivery (line B), and CRP level, maternal temperature at delivery, and WBC count (line C). Sensitivity, specificity, positive predictive value, and negative predictive value were also determined for patients with CRP values greater than 5 mg/dL.

According to one systematic review,⁹ a wide range of CRP values had been used as cutoff values for CAM and PPRM. We chose to use a value at the lower end to yield a broader range, which could later be stratified if we noted statistically significant values, wherein $P < .05$. Spearman rank correlation was used to determine the association between WBC counts and CRP levels in patients with known PPRM and histologic CAM. A repeated-measures regression—where outcome was a log-transformed CRP result—was performed on data from patients with more than 1 sequential CRP result documented after PPRM and before delivery. This was done to evaluate if CRP levels increased over time before delivery in patients with documented histologic CAM.

The secondary analysis—performed after we completed medical record review and defined clinical CAM

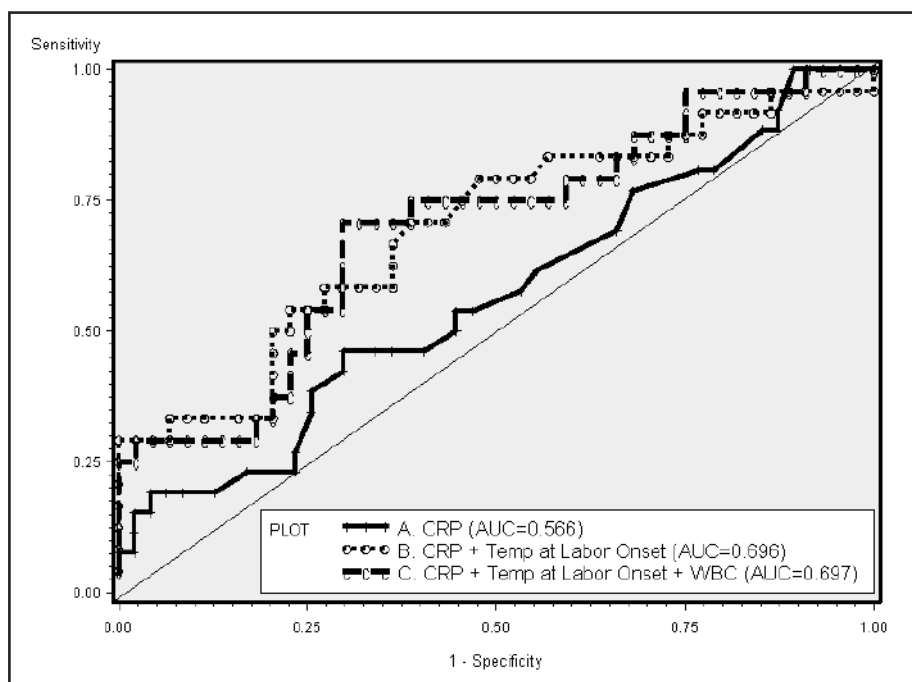


Figure. Depiction of receiver operating curves evaluating laboratory and clinical elements of patients with preterm premature rupture of membranes (N=73). Each receiver operating curve demonstrates performance of the logistic regression model. Lines A, B, and C represent C-reactive protein (CRP) level alone (area under the curve [AUC]=0.566), CRP level and temperature at onset of delivery (AUC=0.696), and CRP level, temperature at onset of delivery, and white blood cell (WBC) count (AUC=0.697), indicating that each is 57%, 70%, and 70% predictive of positive chorioamnionitis status, respectively.

status—investigated the characteristics among patients with clinical CAM, histologic CAM, and non-CAM (ie, control patients). For this analysis, we used the CRP level just before the clinical diagnosis of CAM to assess the possible relationship between CRP levels and clinical CAM. The final CRP level recorded before delivery allowed us to assess any relationship between CRP levels and histologic CAM and to compare CRP levels to those in our control group (non-CAM). Statistical methods for the secondary analysis mirrored the primary analysis except for 1 additional test: a multivariable Cox regression model was fit with CRP level change as the main predictor to investigate the change in CRP level and development of clinical CAM. Clinical CAM status was modeled from the date of PPROM. Patients who did not develop clinical CAM were censored at delivery date.

Results

Overall, 73 patients met inclusion criteria during the 4-year study period. This population was divided into patients with a diagnosis of CAM confirmed at placental pathologic evaluation (n=26) and patients without CAM confirmation (n=47). Most women were white (94.5%), had a mean (SD) age of 28 (6) years, and had singleton gestations (78.1%). No statistically significant difference was observed in CRP levels, days of pregnancy latency, WBC count, smoking status, antibiotic administration, or steroid benefit. The patients with CAM did, however, deliver at earlier gestational ages than patients without CAM, with a mean (SD) age of 29.5 (4.4) weeks compared with 31.9 (3.5) weeks ($P=.02$), respectively (Table).

patients with CAM and patients without CAM. The CRP values evaluated for this analysis were also from the blood sample taken closest to time of delivery. We found a statistically significant difference ($P<.001$) in positive placental culture growth in patients with clinical CAM (34.6%) compared with patients without clinical CAM (6.4%). In addition, patients who developed CAM had a significantly higher temperature at delivery on average than patients who did not develop CAM (98.5°F vs 98.2°F; $P=.02$).

Lines A through C on the Figure depict all the ROC curves and estimated AUC results for each of the logistic models. Although the AUC for CRP level alone is low at 0.566, the AUC after addition of the temperature at onset of delivery jumps to 0.696, which is approximately 70% predictive of CAM status. However, the AUC does not increase significantly with the addition of WBC count. Sensitivity was 76.9% for histologic CAM—determined by a CRP level of greater than 5 mg/dL—specificity was 31.9%, positive predictive value was 38.5%, and negative predictive value was 71.4%. The Spearman correlation between CRP level and WBC count ($r=0.48$) shows a moderate, positive correlation. Therefore, as CRP levels increased, so did WBC counts.

The repeated-measures analysis of patients with clinical CAM before delivery (median [IQR] number of CRP results per patient, 4 [3-7]) resulted in each additional CRP result having an estimated increase of 1.06 ($P=.06$). The CRP result also appeared to increase in patients in the histologic CAM group. This analysis, however, was performed only in the smaller subset of patients (17 of 26 patients) who had sequential CRP results. We concluded that there was

With evaluation of our primary outcome, we observed no statistically significant difference in CRP levels ($P=.32$) between

not enough power in the low sample size of 17 to reach statistical significance.

Results from the secondary analysis—which compared the characteristics among patients with clinical CAM, histologic CAM, or non-CAM—revealed several differences. The clinical CAM group had the lowest average gestational age but were the most likely to have the highest median CRP level, with Gram stain and culture testing positive for bacteria. The histologic CAM group data were similar to the non-CAM group regarding gestational age. The histologic data revealed, however, elevated median CRP levels with Gram stain and culture testing positive for the presence of bacteria compared with the non-CAM group (although still lower than the clinical CAM group). Our multivariable Cox regression model was designed to predict clinical CAM from the date of PPRM, set to censor at delivery date. Change in CRP was the main predictor, measured from PPRM to closest CRP level before clinical CAM or delivery. After adjusting for gestational age, the estimated hazard ratio for CRP change was 1.05 (95% confidence interval, 1.02-1.08; $P=.001$). Therefore, the increased CRP levels from PPRM were statistically significant in predicting clinical CAM development over time.

Comment

Chorioamnionitis is a common infection complicating pregnancy. Although it can occur without rupture of membranes in a subclinical presentation, it is more frequently observed during PPRM. Substantial fetal, neonatal, and maternal morbidity and mortality—including neonatal sepsis, premature birth, cerebral palsy, and postpartum maternal infection—are associated with CAM. Current preventive strategies include prophylactic antibiotic administration at identification of PPRM to reduce potential risk of CAM to both mother and fetus.

The presence of CAM is a risk factor for PPRM.¹⁰ Finding factors that lead to earlier and more accurate diagnosis of CAM and subclinical cases of infection could prove beneficial by reducing the overall morbidity for the fetus or newborn and mother.

The current study investigated the use of CRP level as a serum marker related to CAM and whether CRP levels—either individually or sequentially before delivery—could detect CAM before occurrence of clinical symptoms. Systematic reviews have been published that assessed CRP levels and their ability to predict histologic CAM.¹¹ In this study, we sought to establish a baseline level of

Table.
Characteristics of Patients With PPRM Overall and by Chorioamnionitis Status

Characteristic, No. (%) ^a	All Patients (N=73)	No Chorioamnionitis (n=47)	Chorioamnionitis (n=26)	P Value ^b
Maternal age in years, mean (SD)	28.0 (5.9)	27.8 (5.6)	28.3 (6.5)	.71
White race	69 (94.5)	45 (95.7)	24 (92.3)	.62
Gestational age at delivery in weeks, mean (SD)	31.0 (4.0)	31.9 (3.5)	29.5 (4.4)	.015
Tobacco use	17 (23.9)	10 (21.7)	7 (28.0)	.55
Multiple gestation	16 (21.9)	10 (21.3)	6 (23.1)	.86
Amniocentesis performed	3 (4.1)	1 (2.1)	2 (7.7)	.29
Positive placental Gram stain	5 (6.9)	1 (2.1)	4 (15.4)	.051
Positive placental culture	12 (16.4)	3 (6.4)	9 (34.6)	.003
Steroid administration	57 (79.2)	36 (78.3)	21 (80.8)	.80
Antibiotic administration	71 (97.3)	45 (95.7)	26 (100)	.54
WBC count, $\times 10^9/L$, median (IQR) ^c	11.3 (9.1-15.1)	11.2 (9.0-14.4)	12.9 (10.8-16.1)	.27
CRP level, median (IQR)	9 (5-19)	9 (5-19)	11.4 (6-20)	.34
Temperature at delivery onset, °F, mean (SD) ^d	98.2 (98.1-98.8)	98.2 (97.9-98.5)	98.5 (98.2-99.1)	.021
Latency days, median (IQR)	4 (1-10)	3.3 (1-10)	5 (2-12)	.26

^a All data reported as No. (%) unless otherwise indicated.
^b P value compared patients with chorioamnionitis and patients without chorioamnionitis. Fishers exact or χ^2 tests were used for percentages, 2-sample t test for means, and Wilcoxon rank-sum test for medians.
^c Data were 23% unknown.
^d Data were 7% unknown.

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; PPRM, premature preterm rupture of membranes; SD, standard deviation; WBC, white blood cell.

CRP that would indicate the presence of CAM before clinical symptoms occurred in a population later proven to have CAM at histologic evaluation of the placenta.

Our findings were consistent with previously published outcomes regarding CAM and PPRM. We found that a younger gestational age, on average, was positively associated with the presence of CAM. In addition, as expected, pregnancies with CAM at histologic evaluation were more likely to have positive placental cultures. We did not find a statistically significant difference in the days of latency between those patients with a diagnosis of CAM and those without evidence of CAM.

For patients with CAM in whom 2 or more serial CRP values were obtained, we showed that CRP levels increased continually, though this finding was not statistically significant ($P=.06$). However, when we analyzed the single CRP level closest to delivery in PPRM patients, no predictive level for CAM by CRP level alone was found. Larger study population sizes are necessary to assess whether the rate of rise in serial CRP evaluations is predictive of CAM. Future studies might also assess neonatal sepsis or maternal morbidities.

A logistic model predicting either clinical or histologic CAM from a sole CRP level failed to show a strong correlation. Adding temperature and WBC count moved the model closer to statistical significance, thereby showing no increased benefit for using CRP level alone in predicting CAM. This finding aligns with the findings of van de Laar et al,⁹ who evaluated the accuracy of CRP determination in predicting CAM. Inconclusive data discouraged the investigators from supporting the use of CRP level as a predictor for CAM following PPRM. They also were unable, however, to conclude that CRP was completely ineffective in detecting CAM before the onset of clinical symptoms.

We cannot recommend the routine use of CRP level as an isolated predictor in the treatment of patients with PPRM. However, the reading of CRP level with temperature and WBC counts as combined predictors of histologic CAM is suggestive of a potential complementary role for CRP. We did observe an association of rising CRP levels with histologic CAM. In future studies, investigation of this combination of factors in predicting CAM and assessment of any link to neonatal sepsis could prove beneficial.

Limitations of this study included homogeneous demographics (eg, a predominantly white population). Several traits shown in the literature to be associated with elevated CRP levels—such as lower socioeconomic status, lack of private insurance, and marital status—were not tracked in this study.¹² Further, we did not link neonatal outcomes with predelivery CRP levels.

Conclusion

Many serum markers have been investigated for their roles in the diagnosis and management of PPRM. The usefulness of CRP has come under scrutiny in numerous multistudy reviews, and at least 1 review⁹ concluded that its role in predicting CAM could be neither supported nor ruled out. In our patient population, we saw no evidence of CRP effectiveness as an independent predictor of CAM with individual values tested before delivery. Sequential testing may merit further investigation because patients showed a marked, though not statistically significant, rise in CRP levels before delivery ($P=.06$). The routine use of nonsequential CRP values—whether in predicting CAM or in planning the timing of delivery—is not supported by our study population results.

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