



Original Article



Association of C-Reactive Protein and D-dimer Status with Maternal Outcomes in Pregnant Women with COVID-19

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ABSTRACT

C-reactive protein (CRP) and D-dimer are crucial biomarkers that play a key role in maternal health, helping to assess risks and minimize complications. **Objectives:** To find the association of CRP and D-dimer status with maternal outcomes in pregnant women with COVID-19.

Methods: The prospective cohort study was carried out at the Department of Obstetrics and Gynaecology, Sir Ganga Ram Hospital, Lahore, from July to September 2020. Demographic data, laboratory parameters including COVID-19, D-dimer and CRP levels and maternal outcomes were recorded. Crosstabs and binary logistic regression analyses were performed to measure the risk of adverse maternal outcomes. **Results:** Among 112 COVID-19 suspects, 58 (51.8%) were diagnosed as COVID-19 positive, 82 (73.2%) tested positive for CRP, and 19 (17.0%) were D-dimer positive. COVID-19 positive women exhibited twice the mean D-dimer levels (0.92 ± 1.36 vs. 0.43 ± 0.70 $\mu\text{g/mL}$) and a slightly lower mean CRP level (26.47 ± 31.55 vs. 29.30 ± 32.79 mg/L). Ventilator requirement (32.8% vs. 11.1%) and maternal death rate (29.3% vs. 11.1%) were three times higher in COVID-19 positive cases as compared to the COVID-19 negative cases. CRP positive status and COVID-19 positive showed a statistically significant association and higher risk for ventilator requirement as well as maternal death. However, D-dimer positive status did not show any association with ventilator requirement and maternal death. **Conclusions:** COVID-19 positivity and CRP positivity in pregnant women are associated with adverse maternal outcomes, including increased ventilator requirement and mortality. However, D-dimer positivity was not related to these adverse maternal outcomes.

INTRODUCTION

C-reactive protein (CRP) and D-dimer are crucial biomarkers that play a key role in maternal health, helping to assess risks and minimize complications [1]. CRP, a protein produced by the liver in response to inflammation, serves as an important marker of systemic health issues. Likewise, D-dimer, which results from fibrin breakdown, provides insight into coagulation activity. Elevated levels of these biomarkers have been strongly linked to increased

mortality in patients suffering from COVID-19 [2]. Among pregnant women, these biomarkers act as significant predictors of future health risks, allowing early identification of those who may experience severe complications. Research suggests that CRP and ferritin levels can signal a heightened risk of mortality and the need for intensive medical interventions such as mechanical ventilation [3]. Additionally, CRP levels have been

correlated with conditions like preeclampsia and infections, which negatively impact placental health. These disruptions can lead to complications such as preterm birth and low birth weight, necessitating early monitoring and intervention to protect maternal and fetal well-being [4]. Elevated D-dimer levels in pregnant women indicate potential coagulation disturbances, increasing their vulnerability to serious health conditions. High levels have been associated with a greater likelihood of thromboembolic events, such as deep vein thrombosis and pulmonary embolism, which pose severe risks to maternal health [5]. Coagulation imbalances can also interfere with placental blood flow, potentially leading to fetal growth restriction and placental abruption. Beyond maternal complications, neonates may also be affected, with elevated D-dimer levels linked to conditions such as neonatal sepsis, requiring immediate medical intervention. Recognizing the potential impact of these biomarkers, healthcare providers emphasize the importance of regular monitoring to facilitate timely intervention. Effective management strategies, including anticoagulation therapy and measures to regulate inflammation, help mitigate associated risks. Addressing these biomarkers through proactive medical approaches enhances obstetric care, reducing the likelihood of severe complications and ensuring better health outcomes for both the mother and baby. The COVID-19 pandemic has further emphasized the relevance of CRP and D-dimer in maternal healthcare. Studies indicate that elevated levels of these biomarkers are associated with severe pregnancy complications, including increased hospitalizations, ICU admissions, and higher maternal mortality rates [1, 6]. Despite the growing attention to CRP and D-dimer in predicting disease severity and outcomes in various populations [7], their specific relationship with maternal outcomes in pregnant women affected by COVID-19, particularly within local pregnant populations, remains under-explored.

This study aims to investigate the relationship between these biomarkers and maternal health outcomes in pregnant women diagnosed with COVID-19.

METHODS

The prospective cohort study was carried out at the Department of Obstetrics and Gynaecology, Sir Ganga Ram Hospital, Lahore, from July to September 2020. Ethical approval was obtained from the ethical review committee of Fatima Jinnah Medical University, Lahore, vide reference no. 44-Res-Proposal/CERC dated 16-07-2020. Informed consent was taken from all participants. A total of 112 pregnant women, with symptoms of flu, body pains, cough, and fever, having a history of exposure to coronavirus patients, suspected of COVID-19, and hospitalized during the study period, were included by a non-probability

purposive sampling technique. All those patients who had any potential source of elevated D-dimer, such as family or personal history of H/O venous thromboembolism, were excluded from the study. Similarly, patients with maternal age over 45 years, morbid obesity, patients with recurrent miscarriages, patients with DVT, patients with history of smoking, multiple pregnancies, coagulation disorders, patients on anticoagulant therapy, placental abruption, placenta, women with recent surgery and women with pre-eclampsia and eclampsia were also excluded from the study. All patients underwent detailed history and physical examination, and further management was done in collaboration with the Gynaecology and Medical Departments. A proforma was created to collect demographic information such as patient age, occupation, and education. The number of prenatal visits to the hospital, history of obstetric, perinatal, or postnatal obstetric complications or fetal complications such as preterm birth, intrauterine growth restriction (IUGR), or perinatal death were monitored. Blood specimen was drawn immediately after enrolment in the study to estimate D-dimer and CRP levels, and a nasopharyngeal swab for COVID-19 infection by PCR. Blood for D-dimer level estimation was collected in citrated vacutainers and processed on the same day. Coagulated and hemolyzed specimens were not processed for analysis. All blood specimens were centrifuged and subjected to quantitative estimation of D-dimer based on the chemiluminescence enzyme immunoassay by the PATHFAST [8]. A level of D-dimer ≥ 0.5 $\mu\text{g/mL}$ was taken as positive [9]. The quantitative estimation of CRP level was based on the immunoturbidimetric method by Human Diagnostics [10]. CRP values for pregnant women range from 7-9mg/l depending on gestational age [11]; therefore, CRP level ≥ 10 mg/L was considered positive. The real-time reverse transcriptase-polymerase chain reaction (RT-PCR) method was used for the detection of SARS-CoV-2 RNA in nasopharyngeal swabs by WHO guidelines [12]. All pregnant women were followed up for the incidence of adverse maternal outcomes, including ventilator requirement and mortality during hospitalization. Statistical Package for Social Sciences (SPSS) version 26.0 was used for data analysis. Mean \pm SD was calculated for continuous variables. Frequency (percentage) was calculated for categorical variables, and the chi-square test was used to compare the frequency (percentage) between study groups. Crosstabs and binary logistic regression analyses were performed to calculate odds ratios and adjusted odds ratios with 95% CI. p -value ≤ 0.05 was considered significant.

RESULTS

The age of the studied women ($n=112$) ranged from 20 to 40 years. Women aged ≤ 30 years, with a gestational age of 28-40 weeks and parity ≥ 2 , participated in greater numbers compared to their respective counterparts. Among 112

COVID-19 suspects, 58 (51.8%) were diagnosed as COVID-19 positive, 82 (73.2%) tested positive for CRP, and 19 (17.0%) were D-dimer positive. The overall mean D-dimer level was $0.68 \pm 1.12 \mu\text{g/mL}$, while the mean CRP level was $27.83 \pm 32.04 \text{ mg/L}$. When participants were categorized into COVID-19 negative and positive groups and compared for D-dimer and CRP positive status, COVID-19 positive women had twice the rate of D-dimer positive cases (22.4% vs. 11.1%) and a slightly lower rate of CRP positive cases (70.7% vs. 75.9%). Similarly, COVID-19 positive women exhibited twice the mean D-dimer levels (0.92 ± 1.36 vs. $0.43 \pm 0.70 \mu\text{g/mL}$) and a slightly lower mean CRP level (26.47 ± 31.55 vs. $29.30 \pm 32.79 \text{ mg/L}$) compared to the COVID-19 negative women (Table 1).

Table 1: Baseline Characteristics of Study Population

Baseline Characteristics		Total 112 (100.0%)	COVID 19 Negative 54 (48.2%)	COVID 19 Positive 58 (51.8%)
		n (%)		
Age (Years)	≤30	85 (75.9%)	40 (74.1%)	45 (77.6%)
	>30	27 (24.1%)	14 (25.9%)	13 (22.4%)
Gestational Age (Weeks)	13-28	23 (20.5%)	12 (22.2%)	11 (19.0%)
	28-40	75 (67.0%)	35 (64.8%)	40 (69.0%)
	Postpartum	14 (12.5%)	7 (13.0%)	7 (12.1%)
Parity	≤1	34 (30.4%)	20 (37.0%)	14 (24.1%)
	2-4	55 (49.1%)	23 (42.6%)	32 (55.2%)
	≥5	23 (20.5%)	11 (20.4%)	12 (20.7%)
Antenatal Clinic Registration	Yes	16 (14.3%)	9 (16.7%)	7 (12.1%)
	No	96 (85.7%)	45 (83.3%)	51 (87.9%)
CRP Status	Negative	30 (26.8%)	13 (24.1%)	17 (29.3%)
	Positive	82 (73.2%)	41 (75.9%)	41 (70.7%)
D-dimer Status	Negative	93 (83.0%)	48 (88.9%)	45 (77.6%)
	Positive	19 (17.0%)	6 (11.1%)	13 (22.4%)

Table 2: Risk Factors of Adverse Maternal Outcomes by Cross-Tab Analyses

Variables		Ventilator Required				Maternal Death			
		No	Yes	OR (95% CI)	p-Value	No	Yes	OR (95% CI)	p-Value
CRP Status	Negative	96.7%	3.3%	Ref	0.008	96.7%	3.3%	Ref	0.014
	Positive	70.7%	29.3%	12.0 (1.5-93.1)		73.2%	26.8%	10.6 (1.3-82.8)	
D-dimer Status	Negative	81.7%	18.3%	Ref	0.034	82.8%	17.2%	Ref	0.066
	Positive	57.9%	42.1%	3.2 (1.1-9.3)		63.2%	36.8%	2.8 (0.9-8.2)	
COVID 19 Status	Negative	88.9%	11.1%	Ref	0.012	88.9%	11.1%	Ref	0.032
	Positive	67.2%	32.8%	3.8 (1.4-10.7)		70.7%	29.3%	3.3 (1.1-9.1)	

After adjustment, CRP positive status and COVID-19 positive showed statistically significant association and higher risk for ventilator requirement as well as maternal death. However, D-dimer positive status did not show any association with ventilator requirement and maternal death (Table 3).

Overall, 25 (22.3%) women required a ventilator, and 23 (20.5%) women did not survive. Ventilator requirement (32.8% vs. 11.1%) and maternal death rate (29.3% vs. 11.1%) were three times higher in COVID-19 positive cases as compared to the COVID-19 negative cases (Figure 1).

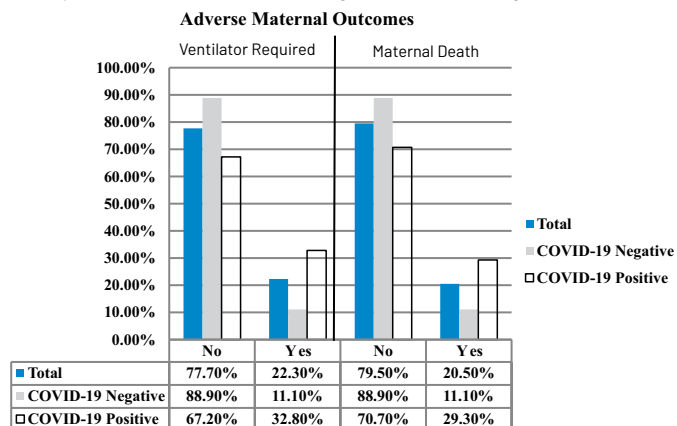


Figure 1: Incidence of Adverse Maternal Outcomes in Women with and without COVID-19

CRP positive status showed statistically significant association and higher risk for both ventilator requirement and maternal death. COVID-19 positive status also showed statistically significant association and higher risk for both ventilator requirement and maternal death. Whereas D-dimer positive status showed statistically significant association and higher risk only for ventilator requirement (Table 2).

Table 3: Risk Factors of Adverse Maternal Outcomes by Binary Logistic Regression Analyses

Variables	Ventilator Required		Maternal Death	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value
CRP Status (Negative/Positive)	13.7 (1.7-110.6)	0.014	11.7 (1.4-93.9)	0.020
D-dimer Status (Negative/Positive)	2.3 (0.7-7.3)	0.159	1.9 (0.6-6.3)	0.253
COVID-19 Status (Negative/Positive)	4.3 (1.4-12.5)	0.007	3.6 (1.2-10.4)	0.019

DISCUSSION

The body's ability to clot blood is impaired by both pregnancy and COVID-19 infection [13]. It is generally accepted that increased levels of D-dimer may be related to poor prognosis in COVID-19 disease, but this aspect is not studied comprehensively in pregnant patients [14, 15]. In current study, it was tried to establish an association between levels of D-dimer and CRP with the clinical condition of COVID-19 pregnant patients. As regards the maternal complications and maternal outcomes regarding CRP Status, D-dimer status and COVID status, it was observed that 96.7% of CRP Negative patients did not require a ventilator, and only 3.3% of these patients required a ventilator. On the contrary, 70.7% of CRP-positive patients did not require a ventilator, and only 29.3% of CRP patients required a ventilator, $p=0.008$. Similarly, when CRP status was correlated with maternal outcome (maternal death), the results showed that 96.7% of patients who were CRP Negative were alive at the end of follow-up, and only 3.3% of patients were dead. On the contrary, among CRP-positive patients, 73.2% were alive and 26.8% were dead. At the end of the follow-up and the results were statistically significant with $p=0.014$. So, CRP-positive patients had a poor prognosis in our study. When we review the literature regarding the association between CRP levels and the prognosis of COVID-19 pregnant patients, there exists a strong correlation. Khalil *et al.*, in their study of 105 pregnant women, quoted that the mean CRP level in these patients was 83.9 ± 103.9 mg/L, and most of the maternal and fetal complications were noted in the third trimester of pregnancy [16]. Another study of 50 COVID-19 pregnant patients documented that 22 (44%) patients showed elevated CRP levels, but no fetomaternal death was reported in this study, although 4 (8%) babies required ICU management and a few babies had physiological jaundice [17]. This may be because they included only mild cases of COVID-19 in pregnant patients in their study. Anter *et al.*, conducted a study between May 2020 and July 2021, including 65 pregnant women. COVID-19 disease was found in 83% of pregnant patients after roughly 5 months of pregnancy. The mean CRP level at admission was 28.86 ± 35.20 . Thrombolytic manifestations, decreased lymphocyte count, and CRP levels at admission predicted ICU admission. The CRP level in ICU-admitted patients was statistically significantly higher than in non-ICU-admitted patients ($p=0.001$) [18]. CRP levels were

elevated in 59% of patients in the early stage of disease in a study of 60 pregnant women. Increased CRP and D-dimer levels were associated with severe pneumonia. The median CRP level in admitted patients was 17.8 mg/L [19]. Maternal and fetal outcomes in pregnant women with COVID-19 were studied by enrolling 105 pregnant women and taking into account measurements such as hemoglobin, TLC, blood ferritin, CRP and blood creatinine. A significant proportion of patients (76.2%) had elevated D-dimer levels. Fetal and maternal complications were assessed in the first, second and third trimesters of pregnancy. The study clearly showed that the mothers faced a more serious problem in the third trimester, with more than 25% of patients requiring a ventilator and two-thirds of patients requiring oxygen therapy [16]. However, in our study, no statistically significant association was established between D-dimer levels and maternal outcome. Another prospective study examined 50 pregnant women who tested positive for COVID-19 at BJ Medical College and Government Hospital, Ahmedabad, between June and October 2020. Across multiple testing sites, D-dimer levels were slightly elevated in 19 (38%) patients. Of the 50 patients, 26 (52%) underwent C section and 23 (46%) were delivered vaginally. There were no maternal or fetal deaths [17]. In this study, fetal and maternal outcomes were favourable; this was probably because most patients had slightly elevated D-dimer, suggesting that D-dimer levels are directly related to fetal and maternal outcomes in pregnant women with COVID-19. A study in Spain, during the first 30 days of the pandemic, published medical records of the first 60 pregnant women infected with COVID-19 between March 14 and April 14, 2020, were reviewed. D-dimer levels were elevated in these patients and associated with severe pneumonia. SVD was detected in 18 women (30%) during the study period, and no maternal deaths were reported [19]. Similar to current's, a study in Iran included 106 pregnant women with COVID-19 in the study. The mean D-dimer value in COVID-19 patients was 852.14 ± 915.08 mg/L, and D-dimer was above the normal range (0-0.5mg/L) in 79.2% of pregnant COVID-19 patients. The most common maternal complications in this study were Cesarean section (31.1%), miscarriage (5.7%) and preterm birth (3.8%) [20].

CONCLUSIONS

It was concluded that COVID-19 positivity and CRP positivity in pregnant women are associated with adverse maternal outcomes, including increased ventilator requirement and mortality. However, D-dimer positivity was not related to these adverse maternal outcomes. These findings highlight the importance of early medical intervention for pregnant women with COVID-19 and CRP positivity to prevent or minimize complications, while emphasizing that D-dimer alone may not be a reliable predictor of adverse maternal outcomes.

Authors Contribution

Conceptualization: SA

Methodology: SA, ZK, UL

Formal analysis: SA, SR, SIM

Writing review and editing: ZK, SH

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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