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Prognostic Value of Serum D-dimer in Predicting Outcomes in COVID-19 Positive Pregnant Women

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Abstract

Background: Combined effects of pregnancy induced hypercoagulability and SARS-CoV-2 infection place pregnant women with COVID-19 disease at high risk of severe outcome. COVID-19 severity has also been associated with serum D-dimer, a biomarker reflecting coagulation and fibrin degradation, in general populations. Despite its prognostic value in pregnant women, the prognostic value of this finding particularly in maternal outcomes remains less understood. The aim of this study was to determine whether elevated serum D-dimer levels in pregnant COVID-19 positive women are of prognostic significance for severe maternal outcomes. ***Methods****:* This retrospective observational study included 62 third trimester COVID 19 positive pregnant women admitted to the Department of Obstetrics and Gynecology, BSMMU, Dhaka from March 2019 to February 2020. Serum D-dimer were measured at admission and day 7, 14. D-dimer levels were related to clinical outcomes and statistically evaluated using chi square tests and logistic regression at $p < 0.05$. ***Results:*** Significantly associated with higher risk of severe outcomes, all of which included ICU admission, respiratory complications and adverse pregnancy events is elevated D-dimer levels (≥1.5 mg/L). In logistic regression analysis, patients with D-dimer levels of ≥1.5 mg/L had 3.5-fold greater odds of severe outcomes (OR 3.486; 95% CI, 1.184 to 10.263; $p = 0.023$). D-dimer had a sensitivity of 64.29%, 67.55% specificity in predicting severe outcomes. ***Conclusion:*** Serum D-dimer is valuable prognostic marker of disease severity in pregnant COVID-19 positive women and may be used for early risk assessment and clinical decision making. Routine measurement may help identify early high risk cases in order to improve maternal outcomes.

Keywords: COVID 19, D dimer, pregnancy, prognostic marker, maternal outcomes.

INTRODUCTION

During the COVID-19 pandemic pregnant women are at risk due to increased risks of severe complications from SARS-CoV-2 infection. Increased plasma volume, altered immune response, and a hypercoagulable state, all occurring during pregnancy, can worsen disease severity. According to data of the Centers for Disease Control and Prevention, pregnant women infected with COVID-19 are more frequently hospitalized, admitted to the ICU and need respiratory support than their nonpregnant peers [1]. Infections by COVID-19 pose an increased risk of developing hypertension, preeclampsia, preterm labor, and fetal complications, which necessitates development of biomarkers that can prognosticate disease severity in COVID-19 infected pregnant women to provide guidance on clinical management and improve outcomes [2].

D-dimer, a fibrin degradation product that reflects coagulant activity, is becoming a potential prognostic marker of severe COVID-19 outcomes. Elevated D-dimer levels have also been linked to

increased thrombotic events and worsened clinical outcomes including mortality [3]. In COVID-19-positive pregnancies, this risk is compounded by pregnancy's inherent hypercoagulable state, potentially leading to a higher incidence of thrombotic complications such as deep vein thrombosis, pulmonary embolism, and even disseminated intravascular coagulation [4,5]. Given these risks, D-dimer may serve as a valuable biomarker in assessing the severity of illness and guiding the clinical management of pregnant women with COVID-19 [6].

In COVID-19, elevated D dimer has been associated with both inflammation and endothelial dysfunction, both critical to the disease's pathogenesis. D-dimer levels have been demonstrated to correlate with disease severity and are elevated in the presence of a high risk for ICU admission and in hospital mortality; studies also show that COVID-19 patients with higher D-dimer levels have a markedly increased risk of adverse outcomes [7]. Huang *et al.,* conducted a meta-analysis that revealed COVID-19 patients with higher D-dimer levels have heightened risk of adverse outcomes. Additionally, sequential measurement of D-dimer levels can help clinicians follow the course of disease and initiate timely intervention [5,8].

This study explored the potential to use serum D-dimer levels in COVID-19 positive pregnant women as prognostic for maternal outcomes with severe prognosis, such as admission to the intensive care unit, need for mechanical ventilation, and adverse pregnancy events. Serum D-dimer could be a reliable marker to identify pregnant women at increased risk of severe COVID-19 outcomes to inform clinical decision making, we hypothesize. Integration of D-dimer testing into routine clinical assessment in pregnant women with COVID-19 improves maternal-fetal outcomes and also enhances resource allocation in COVID-19 maternity care.

OBJECTIVE

The objective of this study was to assess the prognostic value of serum D-dimer levels in predicting severe outcomes in COVID-19-positive pregnant women.

METHODOLOGY & MATERIALS

This retrospective observational study was conducted in the Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from March 2019 to February 2020. Total 62 COVID-19-positive pregnant women in their third trimester who met inclusion criteria and were admitted to the COVID-19 ward are selected through purposive sampling method.

Inclusion criteria

1. Pregnant women in their third trimester of pregnancy admitted with moderate to severe symptoms of COVID-19 (respiratory tract or blood specimen positive for SARS-CoV-2 by RTPCR assay).
2. Patients with percent saturation of oxygen in the blood ≤92% in room air and fulfilling other hospital admission criteria.
3. Patients those was agreed to give informed consent to take part in this study.

Exclusion criteria

1. Patients requiring immediate ICU/CCU at hospital admission (critically ill patients at admission).
2. Patients on previous oral anticoagulants or intravenous heparin.
3. Diagnosed case of chronic liver disease, peripheral vascular disease, cancer, hematologic malignancy, thyroid disorder, autoimmune diseases.
4. History of recent surgery or trauma.

Data collection: Data were collected through structured interviews and hospital records, ensuring informed consent was obtained from all participants. Blood samples were drawn on days 1, 7, and 14 of admission for serum D-dimer analysis, using a commercially available latex kit.

Ethical consideration: Ethical clearance was obtained from BSMMU's Institutional Review Board, ensuring participant confidentiality and the right to withdraw without consequence.

Statistical analysis of data: Data were analyzed using SPSS v22. Descriptive statistics, chi-square tests, and logistic regression were performed to evaluate the relationship between serum D-dimer levels and clinical outcomes. Statistical significance was set at a p-value of <0.05.

RESULTS

Table 1: Comparison of the respondents according to serum D-dimer and CRP levels (n = 62)

Parameters	Group I (n = 28)	Group II (n = 34)	P-value
S. D-dimer level (mg/l)			0.001a
Mean ± SD	3.02 ± 2.69	1.28 ± 0.85	
S. CRP level (mg/dl)			0.035a
Mean ± SD	47.84 ± 29.72	32.41 ± 25.77	

a = unpaired t-test

There was significant association found between outcome of the COVID-19 on the basis of serum D-dimer and serum CRP level ($p<0.05$). Mean serum D-dimer and serum CRP level was higher in severe to critical group (group I) than that of mild to moderate group (group II) ($p<0.05$).

Table 2: Distribution of the respondents according to serum D-dimer cut-off value in respect to adverse outcomes (n = 62)

Adverse maternal outcomes	Serum D-dimer ≥1.5 mg/l (n = 28)	Serum D-dimer <1.5 mg/l (n = 34)	P-value
Required ICU admission	8 (27.6%)	5 (15.2%)	0.230[b]
Preterm delivery	4 (13.8%)	3 (9.1%)	0.696[c]
Preeclampsia	7 (24.1%)	3 (9.1%)	0.167[c]
HELLP Syndrome	1 (3.4%)	0 (0.0)	0.468[c]
Venous Sinus Thrombosis	0 (0.0)	1 (3.0%)	1.000[c]
Death due to covid pneumonia	1 (3.4%)	0 (0.0)	0.468[c]

Multiple response table. b = chi-square test, c = fisher's exact test

In table 2, no significant association was found between serum D-dimer level and adverse outcomes of respondents (COVID-19) ($p>0.05$).

Table 3: Distribution of clinical parameters of severity index according to serum D-dimer cut-off level of 1.5 (n = 62)

S. D-dimer level (mg/l)		Clinical parameters	Group I (n = 28)	Group II (n = 34)	P-value
Chest X-ray findings	≥1.5	Bilateral infiltrate	15 (83.3)	2 (18.2)	0.001[c]
		Normal	3 (16.7)	9 (81.8)	
	<1.5	Bilateral infiltrate	8 (80.0)	2 (8.7)	<0.001[c]
		Normal	2 (20.0)	21 (91.3)	
Respiratory rate (breaths/min)	≥1.5	Brady or tachypnoea	14 (77.8)	1 (9.1)	<0.001[b]
		Normal	4 (22.2)	10 (90.9)	
	<1.5	Brady or tachypnoea	9 (90.0)	4 (17.4)	<0.001[c]
		Normal	1 (10.0)	19 (82.6)	
SpO_2	≥1.5	< 94%	19 (82.6)	0 (0.0)	0.012[c]
		≥ 94%	10 (55.6)	11 (100.0)	
	<1.5	< 94%	1 (10.0)	0 (0.0)	0.303[c]
		≥ 94%	9 (90.0)	23 (100.0)	
Pulse rate (beat/min)	≥1.5	Brady or tachycardia	1 (5.6)	0 (0.0)	1.000[c]
		Normal	17 (94.4)	11 (100.0)	
	<1.5	Brady or tachycardia	1 (10.0)	0 (0.0)	0.303[c]
		Normal	9 (90.0)	23 (100.0)	
Temperature (°C)	≥1.5	Hypo or hyperthermia	9 (50.0)	0 (0.0)	0.005[c]
		Normal	9 (50.0)	11 (100.0)	
	<1.5	Hypo or hyperthermia	6 (60.0)	3 (13.0)	0.010[c]
		Normal	4 (40.0)	20 (87.0)	

b = chi-square test, c = fisher's exact test

Table 3 shows, there was significant association between chest x-ray findings and severity of disease (COVID-19). Among the respondents with D-dimer level more than 1.5 mg/l bilateral lung infiltration, Brady or tachypnoea, SpO2 < 94%, Brady or tachycardia and Hypo or hyper-thermia was higher in higher to critical group than that of mild to moderate group ($p<0.05$).

Table 4: Distribution of biochemical parameters of severity index according to cut-off value for serum D-dimer of 1.5 (n = 62)

S. D-dimer level (mg/l)		Biochemical parameters	Group I (n = 28)	Group II (n = 34)	P-value
Platelet count	≥1.5	<100 X 10^9 /L	1 (5.6)	0 (0.0)	1.000[c]
		≥100 X 10^9 /L	17 (94.4)	11 (100.0)	
	<1.5	<100 X 10^9 /L	0 (0.0)	1 (4.3)	1.000[c]
		≥100 X 10^9 /L	10 (100.0)	22 (95.7)	

S. D-dimer level (mg/l)		Biochemical parameters	Group I (n = 28)	Group II (n = 34)	P-value
Lymphocyte count	≥1.5	<1000 / cmm^3	3 (16.7)	4 (36.4)	0.375^c
		≥1000 / cmm^3	15 (83.3)	7 (63.6)	
	<1.5	<1000 / cmm^3	1 (10.0)	4 (17.4)	1.000^c
		≥1000 / cmm^3	9 (90.0)	19 (82.6)	

b = chi-square test, c = fisher's exact test

Table 4 shows that, no signification association was found between platelet count, Lymphocyte count and severity of disease (COVID-19) (p≥0.05).

Table 5: Diagnostic accuracy of serum D-dimer level in the detection of severity of disease in pregnant women with COVID-19 infection (n = 62)

Statistics	Value	95% CI
Sensitivity	64.29%	44.07% to 81.36%
Specificity	67.55%	49.47% to 82.61%
PPV	62.11%	48.38% to 74.14%
NPV	69.66%	57.02% to 79.90%
Accuracy	66.13%	52.99% to 77.67%

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate of maternal serum D-dimer level in prediction of severity of COVID-19 illness was 64.29%, 67.55%, 62.11%, 69.66% and 66.13%, respectively.

Table 6: Comparison of COVID-19 severity by maternal serum D-dimer and CRP levels between the outcome groups (logistic regression)

Attribute		Coefficient (B)	S.E.	AOR	95% CI for OR		p-value
					Lower	Upper	
Maternal serum CRP level	<47 mg/dl						
	≥47 mg/dl	0.912	0.559	2.49	0.832	7.447	0.103
Maternal serum D-dimer level	<1.5 mg/l						
	≥1.5 mg/l	1.249	0.551	3.486	1.184	10.263	0.023

Binary logistic regression was performed to find out the diagnostic tools associated with severity of disease (COVID-19). The final model contained two independent variables (maternal serum CRP level and maternal serum D-dimer level). As shown in table 6, only two of the independent variables made a unique statistically significant contribution to the model (maternal serum CRP level and maternal serum D-dimer level). The best predictor of severity of disease (COVID-19) (p=0.02) was level of maternal serum D-dimer. The odds ratio for maternal serum Ddimer level indicated that participants who had D-dimer level ≥1.5 mg/l were about 3.486 times more likely to suffer from higher to critical adverse outcome of disease (OR = 3.486, 95% CI 1.184-10.263). It also revealed that maternal serum CRP level (OR = 2.490, 95% CI 0.832–7.447; p-value = 0.103) was the other important diagnostic tools in determining the severity of disease (COVID-19).

DISCUSSION

This study evaluated the prognostic value of serum D-dimer and C-reactive protein (CRP) levels in determining disease severity among COVID-19-positive pregnant women. Elevated D-dimer and CRP levels, as presented in Table 1, were significantly associated with the severe-to-critical outcome group compared to the mild-to-moderate group ($p < 0.05$). These findings are in line with prior studies demonstrating that elevated D-dimer levels correlate with poor prognosis in COVID-19 patients, particularly among those in advanced stages of pregnancy [4,5]. The hypercoagulable state of pregnancy, combined with COVID-19-induced inflammation, likely contributes to this elevation, exacerbating the risk of adverse maternal and neonatal outcomes.

When analyzing D-dimer levels using a 1.5 mg/L cut-off, Table 2 shows a non-significant association between elevated levels and specific adverse pregnancy outcomes, such as ICU admission and preeclampsia. Although patients with D-dimer ≥1.5 mg/L had more frequent occurrences of adverse outcomes, statistical significance was not reached ($p > 0.05$). This trend is consistent with previous findings that elevated D-dimer, while indicative of systemic inflammation, does not always predict specific complications in pregnancy, suggesting that additional factors may influence these outcomes [3,7]. Studies have also reported variability in the predictive power of D-dimer due to individual factors such as baseline health status and comorbid conditions.

The examination of clinical parameters related to disease severity in Table 3 shows significant associations between elevated D-dimer levels and compromised respiratory function, including bilateral lung infiltrates, altered respiratory rates, and low SpO2 levels ($p < 0.05$). These results indicate a potential link between high D-dimer levels and respiratory compromise, an association that has also been noted in studies on respiratory distress in COVID-19 patients, where imaging findings reflect the degree of respiratory failure [9,10]. In contrast, biochemical parameters, such as platelet and lymphocyte counts, did not show significant associations with D-dimer levels (Table 4), suggesting that D-dimer's utility lies more in predicting respiratory severity rather than hematologic changes. This finding is consistent with research highlighting that platelet and lymphocyte levels are less consistent indicators of COVID-19 severity [2,6].

The diagnostic accuracy of D-dimer in predicting severe disease was presents in table 5, with a sensitivity of 64.29% and specificity of 67.55%, yielding positive and negative predictive values of 62.11% and 69.66%, respectively. This moderate accuracy suggests that while D-dimer is valuable for identifying high-risk cases, its limitations necessitate supplementary markers for comprehensive risk assessment [11]. Previous studies recommend using D-dimer in combination with other biomarkers like CRP, which can enhance diagnostic accuracy for detecting severe COVID-19, especially in pregnant populations where physiological changes may affect D-dimer's predictive power [12].

Logistic regression analysis in Table 4.6 shows that D-dimer levels ≥1.5 mg/L significantly predict severe disease outcomes, with an odds ratio of 3.486 ($p < 0.05$). Although CRP also trends toward significance, it does not reach a statistically significant level in this analysis. D-dimer's role as an independent predictor of severe disease in this cohort is consistent with global findings, which underscore its value in clinical stratification and management of COVID-19 in pregnancy [13,14]. The role of both D-dimer and CRP in predictive modeling has been advocated by several studies, particularly as D-dimer reflects thrombotic activity and CRP indicates systemic inflammation, both of which are critical to COVID-19 pathophysiology in pregnancy.

Our study is consistent with trends found in comparative studies showing that elevated D dimer (>2.0 mg/L) can indicate ICU admission and worsen mortality risk in general COVID-19 populations [15]. It is widely accepted that a COVID 19 inflammatory signal activates coagulation pathways leading to fibrin degradation and the release of D dimer, which is a reliable, if non specific, marker to identify severe cases in pregnant women and where D dimer may further increase in the presence of a hyper.

In light of these hypercoagulable state of pregnancy, pregnant women infected with COVID-19 are even prone to thrombotic complication and elevated D dimer level would further increase their risk [17]. Our results suggest that D dimer may act as an easily and accurately measurable denominator for more severe disease, considering moderate sensitivity and specificity, yet D dimer should be incorporated in clinical settings with other markers such as CRP.

CONCLUSION

This study concludes that elevated serum D-dimer levels are a significant predictor of adverse outcomes in COVID-19-positive pregnant women, suggesting its potential as a prognostic marker. Findings support the use of D-dimer as part of a comprehensive risk assessment tool to improve early interventions.

LIMITATION AND RECOMMENDATION

The study was conducted in a single hospital with a small sample size which may affect generalizability. It is recommended that serum D-dimer measurement be routinely incorporated into COVID-19 patient assessments, particularly for pregnant women. Further studies should explore the efficacy of integrating D-dimer testing with other biomarkers for improved prognostic accuracy in high-risk maternal cases.

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